2

## WORLD INTELLECTUAL, PROPERTY ORGANIZATION INTELLECTUAL, PROPERTY ORGANIZATION



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

	(10 x) 1 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x 2 x
(51) International Patent Classification 7:	(11) International Publication Number: WO 00/47568
C07D 281/02, A61K 31/55, A61P 3/06, A2 C07D 417/12	(43) International Publication Date: 17 August 2000 (17,08,00)
(21) International Application Number: PCT/USO0/02503	(81) Designated States: AB, AL, AM, AT, AU, AZ, BA, BB, BG,
(22) International Füing Date: 10 February 2000 (10.02.00)	
(30) Priority Data: 60/119,933 12 Pebruary 1999 (12.02.99) US	
(71) Applicant (for all derignated States except US); G.D. SEARLE & CO. (US/US); Corporate Patent Department, 5200 OM Orchard Road, Stokie, IL 60077 (US).	AZ, BY, KQ, KZ, MĎ, RU, TJ, Thộ, Bượcen patrant (AT, BR, CY, OB, DK, ER, SP, RR, GB, GR, IE, TT, LU, MC, MI, PT, SB, OAPI patrant (BF, BJ, CP, CO, CJ, CM, GA, GH, GW, GM, GW, ML, MR, NB, SN, TD, TO).
(73) Inventors; and (for US only): TOLLEFSON, Michael, (75) Inventors/Applicants (for US only): TOLLEFSON, Michael, B. (1902): 373 Big Hom Drive, Hainesville, IL 60030 (18): ACLODZIBJ, Seve, A. (19340); 2448 Chipon Road, Ballwin, MO 63021 (US). REITZ, David, B. (USUS); 14814 Pleasant Ridge Court, Chesterfield, MO 63017 (US).	Published Wilhout international tearth report and to be republished upon receipt of that report.
(74) Agenis: WARNER, James, M. et al.; G.D. Searie & Co., Corporate Patent Department, 5200 Old Orchard Road, Skokie, IL 60077 (US).	
(54) Title: NOVEL 1,2-BENZOTHIAZEPINES HAVING ACTI	(\$4) TIUE: NOVEL 1,2-BENZOTHIAZEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILB ACID TRANSPORT AND TAUROCHOLATB UPTAKB

# FOR THE PURPOSES OF INFORMATION ONLY

Novel 1,2-benzohlazapires, derivatives and analogs thereof, pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis analor treatment of hyperlipidemic diseases, conditions analor disorters, such as those associated with albertacterosts analor hypertholesterolemia.

(57) Abstract

il.

Albania	2	Spain	2	Lesotho	55	Slovenia
Amesia	<b>E</b>	Plaberd	5	Uthranila	×	Slovatla
Austria	E	Prance	3	Luxembourg	Z	Scoregal
Ametralia	ð	Gathon	2	Levis	28	Swarlland
Azzrbeijen	8	United Kingdom	MC	Monace	£	
Bosnis and Herzegowins	S	Occupia	æ	Republic of Moldova	2	200
Berbados	H	Chara	MG	Madaraca	2	Thilliam
Belghun	3	Outhea	M	The former Yugoslav	Ē	Turkmenistra
Burtina Paso	5	Опессе		Republic of Macedonia	Ĕ	Tetay
Bulgaria	2	Hongary	Æ	Mali	F	Thirthad and Tobaro
Benin	*	frehand	W	Mongolia	ž	Utralpe
Brutil	ď	brud	M	Maurtania	3	Uganda
Beltrus	23	Profited	MUM	Malawi	3	United States of America
Chands	E	Raly	MX	Mexico	5	Urbehlsten
Central African Republic	4	Apre	X	Niger	š	Vict Ness
Congra	Ä	Kenya	ź	Netherlands	2	Yusoslavia
Switzerland	2	Kyrgyzetse	2	Norway	A2	Zimbabwa
Côte d'Ingire	2	Democratic People's	77	New Zealand		
Cumeroon		Republic of Kores	7	Polend		
O.	ğ	Republic of Korea	E	Portugal		
Cabe	2	Karatum	RO	Romania		
Croch Republic	ន	Saint Lucis	BC	Russian Pederation		
Остану	3	Liechtenstein	8	Sudan		
Demnerk	3	Sri Lanks	18	Sweden		
Betonia	2	Derle	٥			

#### NOVEL 1,2-BENZOTHIAZEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

#### Field of the Invention

treatment of hyperlipidemic diseases, conditions and/or disorders, such as them, and their use in medicine, particularly in the prophylaxis and/or derivatives and analogs thereof, pharmaceutical compositions containing those associated with atherosclerosis and/or hypercholesterolemia, in The present invention relates to novel 1,2-benzothiazepines,

### Description of Related Art

5

ᅜ

physiology and known active agents relating to bile acids and cholesterol Biophysica Acta, 1210 (1994) 255-287, discusses the biochemistry, Nonsystemic Agents Having Hypocholesterolemic Properties," Biochimica et atherosclerosis. Stedronsky, "Interaction Of Bile Acids And Cholesterol With which indicates such reduction leads to an improvement in the disease state of cholesterol in a causal relationship. Epidemiological data has accumulated within the lumen of the intestinal tract is found to reduce the levels of scrum particularly atherosclerosis. Interfering with the circulation of bile acids ("LDL") cholesterol are major risk factors for coronary heart disease and elevated concentrations of total cholesterol and low-density lipoprotein It is well-settled that hyperlipidemic conditions associated with

20

interruption of the enterohepatic circulation of bile acids in humans in Heubi, Bile Acid Transport", Gastroenterology, 1982:83:804-11. J.E., et al., "Primary Bile Acid Malabsorption: Defective In Vitro Iteal Active

Pathophysiologic alterations are shown to be consistent with

25

al, in "Regulation of Hepatic Cholesterol Metabolism In Humans: Stimulatory thereby interfering with their normal enterohepatic circulation. Reihnér, E. et Effects Of Cholestyramine On HMG-CoA Reductase Activity And Low In fact, cholestyramine binds the bile acids in the intestinal tract,

- cholesterol and decreases serum LDL cholesterol levels. Suckling el al, upregulation of the liver LDL receptors which enhances clearance of liver bile acid synthesis by the liver using cholesterol as well as an Density Lipoprotein Receptor Expression In Gallstone Patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226. This results in an increase in
- 10 "Cholesterol Lowering And Bile Acid Excretion In The Hamster With discloses the results of cholestyramine treatment to lower serum cholesterol Cholestyramine Treatment", Atherosclerosis, 89(1991) 183-190), also

2 ileal bile acid transport system is a putative pharmaceutical target for the 268, No. 24, Issue of August 25, pp. 18035-18046, 1993. "Intestinal Bile Acid Absorption", The Journal of Biological Chemistry, Vol. enterohepatic circulation with specific transport inhibitors. Kramer, et al, treatment of hypercholesterolemia based on an interruption of the In another approach to the reduction of recirculation of bile acids, the

- ß 20 as hypocholesterolemic agents. See, e.g., Canadian Patent Application Nos. physiological bile acid transport with the goal of reducing the LDL cholestero circulation system and their derivatives, including bile acid, which inhibit the polymers of various naturally occurring constituents of the enterohepatic 379 161; 0 549 967; 0 559 064; and 0 563 731 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 level sufficiently to be effective as pharmaceuticals and, in particular for use In a series of patent applications, Hoechst Aktiengesellschaft discloses
- hypolipidemic activity in The Wellcome Foundation Limited disclosure of the In vitro bile acid transport inhibition is disclosed to show

PCT/US00/02503

\_

world patent application number WO 93/16055 for "Hypolipidemic Benzothiepine Compounds".

Selected benzothiepines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

S

Additional benzothiepines for use as hypolipidemic agents are disclosed in WO97/33882 and U.S. Patent 5,994,391.

Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

2

WO96/16051 published May 30, 1996 describes certain 1,5-benzothiazepines as useful in the treatment of hyperlipidemic conditions.

15

WO96/05188 published February 22, 1996 describes certain 1,4-benzothiazepines as useful in the treatment of hyperlipidemic conditions.
Additional benzothiazepines are discussed in the references set forth

below. These references either do not disclose a specific utility or disclose a

different utility than the present invention.

Orahovats et al., "A Ring Enlargement From Seven- To TenMembered-Ring Sulfonamide Derivatives", <u>Helv. Chim. Acta.</u> vol. 79, pp.
1121-1128 (1996) describes 4,5-dihydro-7,8-dimethoxy-1,2-benzothiazzpine3-one-1,1-dioxide.

Katrizky et al., "Preparation Of 6., 7- and 8-Membered Sultams By
Friedel-Crafts Cyclization Of &-Phenylalkanesulfamoyl Chlorides", <u>Org.</u>

<u>Prep. Proced. Int.</u>, vol. 24(4), pp. 463-467 (1992) describes 2,3,4,5-tetrahydro-1,2-benzothiazepine-1,1-dioxide and 2,3,4,5-tetrahydro-2-butyl-1,2-benzothiazepine-1,1-dioxide for possible use as an anticonvulsant, diuretic or sedative.

Beckwith et al., "Iododediazoniation Of Arenediazonium Salts Accompanied By Aryl Radical Ring Closure", <u>I. Org. Chem.</u> vol. 52, pp. 1922-1930 (1987) describes 2,3,4,5-tetrahydro-2-allyl-1,2-benzothiazepine-1,1-dioxide.

Stassinopolou et al., "JC NMR Spectra Of Benzothiazepine,
Benzothiazone and Benzosulphonamide N-substituted Derivatives", <u>Org.</u>

<u>Magn. Reson.</u>, vol. 21(3), pp. 187-189 (1983), describes certain N-substituted
4,5-dihydro-7,8-dimethoxy-1,2-benzothiazepine-3-one-1,1-dioxides.

Tamura et al., "Novel Conversions Of Benzo[b]thiophen-3(2H)-ones

Into 1,2-Benzisothiazole And Tetrahydro-1,2-benzothiazepin-5-One Systems
Via Sulphimide Intermediates", J. Chem. Soc., Perkin Trans. L. vol. 12, pp.
2830-2834 (1980) describes 2,3,4,5-tetrahydro-2-tosyl-4-methyl-1,2-benzothiazepine-5-one-1,1-dioxide.

Catsoulacos et al., "Synthesis Of Some N-Substituted 4,5-Dibydro-7,8-dimethoxybenzothiazepin-3-one 1,1-Dioxides, <u>I. Hetero, Chern.</u> vol. 13(6), pp. 1309-1314 (1976) describes 4,5-dibydro-7,8-dimethoxy-1,2-benzothiazepine-3-one-1,1-dioxide and certain 4,5-dibydro-2-(phenyl, substituted phenyl or pyridyl)-7,8-dimethoxy-1,2-benzothiazepine-3-one-1,1-dioxides having anti-inflammatory and central nervous system activity.

Pangiotopoulos et al., "N(p-Bromopheny!)-4,5-Dihydro-7,8-Dimethoxy Benzothiazepine-3-One 1,1-Dioxide C<sub>1</sub>,H<sub>1</sub>,BrNO<sub>5</sub>S", <u>Cryst. Struct. Comm.</u>, vol. 9, pp. 313-320 (1980) describes 4,5-dihydro-2-(4-bromopheny!)-7,8-dimethoxy-1,2-benzothiazepine-3-one-1,1-dioxide.

Catsoulacos et al., "Thiazo Compounds: Derivatives Of 4,5-Dihydro-7,8-Dimethoxybenzothiazepin-3-one 11-Dioxides", <u>I. Chem. Eng. Data.</u> vol. 22(3), pp. 353-354 (1977) describes 4,5-dihydro-2-(ethyl, n-propyl or isopropyl)-7,8-dimethoxy-1,2-benzothiazepine-3-one-1,1-dioxide.

Camoutsis et al., "N-Substituted 4,5-Dihydro-1,2-benzothiaepin-3-one 1,1-Dioxide", L. Hetero, Chem. vol. 17(5), pp. 1135-1136 (1980) describes

PCT/US00/02503

one-1,1-dioxides. certain 4,5-dihydro-2-(3- or 5-pyridyl)-7,8-dimethoxy-1,2-benzothiazepine-3-

are described as lipoxygenase inhibitors useful in the treatment of generically encompass certain benzothiazepine compounds. These derivatives U.S. Patent No. 5,350,761 describes hydroxylamine derivatives that

inflammatory and allergic conditions

heterocyclyl)alkyl)-benzothiazepines as useful for controlling micturition. containing-heterocyclyl)alkyl)benzothiazepines and aralkyl-(N-containing-WO98/02432 published January 22, 1998 describes certain 5-(aryl-(N.

5 sulfonylamino-substituted benzothiazepines as inhibitors of the enzyme cyclooxygenase II. WO97/03953 published February 6, 1997 describes certain

compounds are identified as kappa receptor agonists useful as analgesics and diuretics and for the treatment of cerebral ischaemia. benzothiazepines substituted with azacyclic condensed piperazines. These WO95/21843 published August 17, 1995 describes certain

2

benzothiazepine-5-ones useful as muscle relaxants. EP338331 published October 25, 1989 describes certain 2-

### Summary of the Invention

20 that are effective agents for the prophylaxis and/or treatment of hyperlipidemic diseases, conditions and/or disorders. A first aspect of the invention comprises novel 1,2- benzothiazepines

the prophylaxis and/or treatment of hyperlipidemic diseases, conditions and/or compositions comprising the novel 1,2- benzothiazepines that are suitable for A second aspect of the invention comprises pharmaceutical

23

and/or treatment of hyperlipidemic diseases, conditions and/or disorders A third aspect of the invention comprises methods for the prophylaxis

SUBSTITUTE SHEET (RULE 26)

effective amount of one of the novel 1,2- benzothiazepines. comprising administering to a subject a prophylactically or therapeutically

novel 1,2-benzothiazepines of the present invention A fourth aspect of the invention comprises methods of making the

specification of this application. Additional aspects of the invention are discussed throughout the

## Detailed Description of the Invention

the art in practicing the present invention. This detailed description, The following detailed description is provided to aid those skilled in

5 references cited herein, including the contents of the references cited within however, should not be construed to unduly limit the present invention as scope of the present inventive discovery. The contents of each of the made by those of ordinary skill in the art without departing from the spirit or modifications and variations in the embodiments discussed herein can be

corresponding to the structure of Formula (I): Accordingly, the present invention provides compounds 15

these primary references, are herein incorporated by reference in their

wherein:

20

(

Э

PCT/IISOOM2E03

7

q is an integer from 1 to 4;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

 $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen; hydrocarbyl; -OR?; -NR $^9R^{10}$ ; -SR?; -S(O)R?; -SO2R?; and -SO3R?; or

2

 $\rm R^3$  and  $\rm R^4$  together form =0; =NOR  $^9$  ; =S; =NNR  $^9\rm R^{10}$  ; =NR  $^9$  , or =CR  $^{11}\rm R^{12}$  ,

wherein R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino; wherein said hydrocarbyl moieties may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl moieties optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; and

13

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; hydrocarbyl; -OR<sup>9</sup>; -NR<sup>9</sup>R <sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; or R<sup>11</sup> and R<sup>12</sup> together with the carbon atom to which they are

 $\mathbb{R}^5$  and  $\mathbb{R}^6$  are independently selected from the group consisting of

attached form a cyclic ring; and

WO 00/47568

PCT/US00/02503

~

hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl;  $-OR^9$ ;  $-SR^9$ ;  $-S(O)R^9$ ;  $-SO2R^9$ ; and  $-SO3R^9$ ;

wherein the R<sup>5</sup> and R<sup>6</sup> radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -NO2; -CN; oxo; hydrocarbyl; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>1</sup>; -NR<sup>13</sup>C(O)NR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>CO<sub>2</sub>R<sup>14</sup>; -NR<sup>13</sup>CO<sub>3</sub>R<sup>14</sup>; -NR

NR<sup>13</sup>SO<sub>2</sub>NR<sup>14</sup>R<sup>15</sup>, -PR<sup>13</sup>R<sup>14</sup>, -P(O)R<sup>13</sup>R<sup>14</sup>, -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; .

P(OR<sup>13</sup>)OR<sup>14</sup>, -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>; and -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; and

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; or

2

wherein R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycly! that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary sals; or

23

wherein  $R^{\mbox{\scriptsize $1$}4}$  and  $R^{\mbox{\scriptsize $1$}5}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

wherein A is a pharmaceutically acceptable anion, and M is a

pharmaceutically acceptable cation; and wherein R9 is as defined above; or

R4 and R6 together represent a bond; and

 $\mathbb{R}^{N}$  is selected from the group consisting of hydrogen and

or more heteroatoms independently selected from the group consisting of hydrocarbyl optionally may have one or more carbon atoms replaced by one hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with oxygen, nitrogen, sulfur and phosphorus; one or more groups comprising one or more heteroatoms, and wherein said

ᅜ 5  $NR^{1}C(0)R^{13}; -C(0)NR^{13}R^{14}; -C(0)OM; -COR^{13}; -S(0)_{fi}NR^{13}R^{14}; -$ NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>R<sup>14</sup>;-SR<sup>13</sup>;-S(O)R<sup>13</sup>;-S(O)2R<sup>13</sup>;-SO3R<sup>13</sup>;-S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A;consisting of hydrogen; halogen; -CN; -NO2; hydrocarbyl; -OR  $^{13}$ ; one or more  $\mathbb{R}^{X}$  radicals are independently selected from the group

N+R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -PR<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P+R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; amino optionally may have one or more carbon atoms replaced by one or more groups comprising one or more heteroatoms, and wherein said hydrocarby wherein said hydrocarbyl may be optionally substituted with one or more acid residue; peptide residue; polypeptide residue; and carbohydrate residue,

20 nitrogen, sulfur and phosphorus; and heteroatoms independently selected from the group consisting of oxygen

wherein n is 0, 1 or 2; and

wherein R13, R14, R15, A7, and M are as defined above; or

provided that at least one of R1, R2, R3, R4, R5, and R6 is a a pharmaceutically acceptable salt, solvate, or prodrug thereof; and

25

radical other than hydrogen or alkyl; and

radical other than heterocycylalkyl. provided that when R<sup>2</sup> or R<sup>0</sup> is aryl, the other of R<sup>2</sup> and R<sup>6</sup> is a

WO 00/47568

PCT/US00/02503

Formula I wherein: A preferred class of compounds comprises those compounds of

q is an integer from 1 to 4;

heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; hydrogen; alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl;  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of

alkoxyalkynyi; aryloxyalkyi; aryloxyalkenyi; aryloxyalkynyi; heterocylcyloxyalkyl; heterocycloxyalkenyl; heterocyclyloxyalkynyl;

5 alkylaryl; and (polyalkyl)aryl; or  $\mathbb{R}^1$  and  $\mathbb{R}^2$  taken together with the carbon to which they are attached

alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; form C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl; wherein the R<sup>1</sup> and R<sup>2</sup> alkyl; cycloalkyl; alkenyl; cycloalkenyl;

20 15 CO2R9; and -CONR9R10; and. consisting of -CN; halogen; oxo; -OR9; -NR9R10; -N+R9R10RWA; -SR9; may be substituted with one or more radicals selected from the group aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; -S'R'R\0A;-PR\0R\0;-P\R\0R\0R\wA;-S(O)R\9;-SO2R\9;-SO3R\9;heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally

aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; wherein the  $\mathbb{R}^1$  and  $\mathbb{R}^2$  alkyl; cycloalkyl; alkenyl; cycloalkenyl;

consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; SO-; -SO2-; -S $^+$ R $^9$ A-; -PR $^9$ -; -P(O)R $^9$ -; -P $^+$ R $^9$ R $^{10}$ A-; or phenylene; and may have one or more carbons replaced by -O-; -NR  $^9$ -; -N $^+$ R  $^9$ R  $^{10}$ A-; -S-; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally wherein  $\mathbb{R}^9$  ,  $\mathbb{R}^{10}$ , and  $\mathbb{R}^{W}$  are independently selected from the group

25

5

wherein A is a pharmaceutically acceptable anion; and  $R^3$  and  $R^4$  are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; avyl; heterocyclyl; -OR?; -NR^9R^{10}; -SR^9; -S(O)R^9; -SO\_2R^9; and -SO\_3R^9; or

 $\rm R^3$  and  $\rm R^4$  together form =0; =NOR  $^2$  ; =S; =NNR  $^9\rm R^{10}$  ; =NR  $^9$  , or =CR  $^{11}\rm R^{12}$  ,

2

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR<sup>2</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SO)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>2</sub>R<sup></sup>

2

and -CONR  $^9R_1^{10}$ ; or  $R^{11} \text{ and } R^{12} \text{ together with the carbon atom to which they are attached form a cyclic ring, and}$ 

wherein R9 and R10 are as defined above; and

20 R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR<sup>2</sup>; -SR<sup>2</sup>; -S(O)R<sup>2</sup>; -SO2R<sup>2</sup>; and -SO3R<sup>2</sup>;

wherein the R<sup>5</sup> and R<sup>6</sup> alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; arkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; SR<sup>13</sup>; -S(O)R<sup>13</sup>; -S(O)R<sup>13</sup>; -S(O)R<sup>13</sup>; -S(O)R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>14</sup>OR<sup>14</sup>; -NR<sup>14</sup>; -NR<sup>14</sup>; -NR<sup>14</sup>OR<sup>14</sup>; -NR<sup>14</sup>; -NR

23

WO 00/47568

12

CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>CO,R<sup>14</sup>; -NR<sup>13</sup>CO)R<sup>15</sup>; -OC(O)NR<sup>14</sup>R<sup>15</sup>; -NR<sup>13</sup>SO<sub>1</sub>R<sup>14</sup>; -NR<sup>13</sup>SO<sub>1</sub>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P<sup>4</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>15</sup>.

5 P(OR<sup>13</sup>)OR<sup>14</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>T; and -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>T; and wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R³ and R⁴ radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; arkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR 7; -NR 7R 8; -SR 7; -S(O)R 7; -SO2R 7; -SO3R 7; -CO2R 7; -CONR 7R 8; -N\*R 7R 8R 9A; -P(O)R 7R 8; -PR 7R 8; and -P(O)(OR 7)OR 8; and

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R³ and R⁴ radicals optionally may have one or more carbons replaced by -O·; -NR<sup>7</sup>··· N<sup>+</sup>R<sup>7</sup>R <sup>8</sup>A··; or N<sup>+</sup>R<sup>7</sup>R <sup>8</sup>A··; -P·(O)R<sup>7</sup>··· P<sup>+</sup>R<sup>7</sup>R <sup>8</sup>A··; or

13

20 phenylene; and

wherein R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl;

alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylarmoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; aminocarbonylalkyl; arylaminocarbonylalkyl; and polyether, or

22

oxo, carboxy, and quaternary salts; or substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally wherein R13 and R14 together with the nitrogen atom to which they

are attached form a cyclic ring; and wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they

arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl;

alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl;

5

halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; substituted with one or more radicals selected from the group consisting of carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be

ᅜ alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary S<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A-; and carbohydrate residue; and CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PO(OR <sup>16</sup>)OR <sup>17</sup>; -P<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>11</sup>A-; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>w</sup>A<sup>-</sup>;-SR<sup>16</sup>;-S(O)R<sup>9</sup>;-SO<sub>2</sub>R<sup>9</sup>;-SO<sub>3</sub>R<sup>16</sup>;-CO<sub>2</sub>R<sup>16</sup>;heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR 16; -NR 9R 10;

arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl;

20

residue; amino acid residue; peptide residue; or polypeptide residue; and carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may -SO<sub>2</sub>; -S<sup>+</sup>R<sup>9</sup>A<sup>-</sup>; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; -P(O)R<sup>8</sup>-; phenylene; carbohydrate have one or more carbons replaced by -O-; -NR<sup>9</sup>-; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·-; -S-; -SO-; wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

25

WO 00/47568 PCT/US00/02503

74

consisting of R<sup>9</sup> and M; and

alkynyl; aralkyl; and heterocyclylalkyl; and  $\mathbf{R}^{\mathbf{N}}$  is selected from the group consisting of hydrogen; alkyl; alkenyl; wherein R, R, R, R, R, R, and A are as defined above; and wherein M is a pharmaceutically acceptable cation; and

heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy; -OR 13; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl; polyalkyl; one or more RX radicals are independently selected from the group

7 5 polypeptide residue; and carbohydrate residue; S(O)nNR 13R 14; -NR 13R 18; -NR 18 OR 14; -N+R 13R 14R 15A; -PR 13R 14  $\label{eq:coring} {\tt NR^{14}C(O)R^{13}; -C(O)NR^{13}R^{14}; -C(O)OM; -COR^{13}; -OR^{18}; -}$ NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; - ${\tt NR}^{13}{\tt R}^{14}; -{\tt SR}^{13}; -{\tt S}(0){\tt R}^{13}; -{\tt S}(0){\tt 2R}^{13}; -{\tt SO}_{3}{\tt R}^{13}; -{\tt S}^{+}{\tt R}^{13}{\tt R}^{14}{\tt A}; -$ -P(O)R $^{13}$ R $^{14}$ ; -P $^{\dagger}$ R $^{13}$ R $^{14}$ R $^{15}$ A $^{\circ}$ ; amino acid residue; peptide residue;

acyloxy radicals optionally may be further substituted with one or more alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; radicals selected from the group consisting of halogen; -CN; oxo; -OR <sup>10</sup>; wherein the R\* alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl;

20  $P^{+}R^{9}R^{11}R^{12}A^{-}; \; {}_{\cdot}S^{+}R^{9}R^{10}A^{-};$  and carbohydrate residue; and NR9R10; NTR9R10RWA; SR16; S(O)R9; SO2R9; SO3R16; CO2R16; -CONR9R10; -SO2NR9R10; -PO(OR16)OR11; -P9R10; wherein the R\* quaternary heterocyclyl radical optionally may be

25  $SO_2OM; -SO_2NR^{13}R^{14}; -C(O)NR^{13}R^{14}; -C(O)OM; -COR^{13};$ SO2R<sup>13</sup>;-SO3R<sup>13</sup>;-NR<sup>13</sup>OR<sup>14</sup>;-NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>;-CO2R<sup>13</sup>; OM;heterocyclylalkyl; polyether;  $-OR^{13}$ ;  $-NR^{13}R^{14}$ ;  $-SR^{13}$ ;  $-S(O)R^{13}$ ; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; substituted with one or more radicals selected from the group consisting of

PCT/US00/02503

wherein the R<sup>X</sup> radicals comprising carbon optionally may have one or more carbons replaced by -O.; -NR <sup>13</sup>; -N<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A<sup>-</sup>; -S.; -SO.; -SO<sub>2</sub>; -SO<sup>2</sup>; -S<sup>4</sup>R <sup>13</sup>A<sup>-</sup>; -PR <sup>13</sup>; -P(O)R <sup>13</sup>.; -P(D)R <sup>14</sup>; -P<sup>4</sup>R <sup>13</sup>R <sup>14</sup>A<sup>-</sup>; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O.; -NR <sup>9</sup>; -N<sup>+</sup>R <sup>9</sup>R <sup>10</sup>A<sup>-</sup>; -S-; -SO<sub>2</sub>; -S<sup>2</sup>R <sup>9</sup>A<sup>-</sup>; -PR <sup>9</sup>; -P<sup>2</sup>R <sup>9</sup>R <sup>10</sup>A<sup>-</sup>; or -P(O)R<sup>2</sup>; and

wherein R<sup>18</sup> is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and

23

wherein the R<sup>18</sup> alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; NO<sub>3</sub>; oxo; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>4</sup>R<sup>9</sup>R<sup>11</sup>Z<sup>A</sup>; -SR<sup>9</sup>; -SO)R<sup>9</sup>; -SO<sub>2</sub>NR<sup>9</sup>; -CO)R<sup>9</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>9</sup>; -PR<sup>9</sup>R<sup>10</sup>; -PR<sup>9</sup>R<sup>10</sup>; -P(OR<sup>13</sup>)OR<sup>14</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; and -C(O)OM;

2

25

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In the various embodiments of the invention,  $R^3$  and  $R^4$  preferably are independently selected from the group consisting of H; aryl;

9

heterocyclyl; and quaternary heterocyclyl;

wherein the R<sup>5</sup> and R<sup>6</sup> aryl; heterocyclyl; and quaternary heterocyclyl; radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN;

- 5 -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -
- wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,
  alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl,
  heterocyclylalkyl, and polyether substitutents of the R³ and R⁴ radicals
  optionally may be further substituted with one or more radicals selected
  from the group consisting of -CN³, halogen; hydroxy; oxo; alkyl; cycloalkyl;
  alkenyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary
  theterocyclyl; -OR7; -NR7R8. -SR7; -SCOR7; -SCOR7.
- beterocyclyi; -OR7; -NR<sup>7</sup>R<sup>8</sup>, -SR<sup>7</sup>; -S(O)R<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -CO<sub>1</sub>R<sup>8</sup>; -N<sup>4</sup>R<sup>8</sup>R<sup>9</sup>A<sup>8</sup>; -P(O)R<sup>7</sup>R<sup>8</sup>; -PR<sup>7</sup>R<sup>8</sup>; -P<sup>4</sup>R<sup>8</sup>R<sup>9</sup>A<sup>7</sup>; and P(O)(OR<sup>7</sup>)OR<sup>8</sup>; and
- wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polycher substituents of the R³ and R⁴ radicals optionally may have one or more carbons replaced by -O.; -NR<sup>7</sup>;.

  N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A·; -S·; -SO·; -SO<sub>2</sub>···S<sup>+</sup>R<sup>7</sup>A··; -PR<sup>7</sup>·, -P(O)R<sup>7</sup>·; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A··; or phenylene; and

22

wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group

alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the

are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they wherein R13 and R14 together with the nitrogen atom to which they

5

-SO3R<sup>16</sup>; -CO2R<sup>16</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO2NR<sup>9</sup>R<sup>10</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; radicals optionally may be substituted with one or more radicals selected polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl;  $PR^9R^{10}$ ;  $P^+R^9R^{10}R^{11}A$ ;  $S^+R^9R^{10}A$ ; and carbohydrate residue; and guanidinyl; -OR<sup>16</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>-</sup>; -SR<sup>16</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; wherein the  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  alkyl; haloalkyl; cycloalkyl; wherein the R  $^{13}$ , R  $^{14}$ , and R  $^{15}$  alkyl; haloalkyl; cycloalkyl;

8

2

are attached form a cyclic ring; and

25

arylalkyl; heterocyclylalkyl; quatemary heterocyclylalkyl; alkylarylalkyl;

WO 00/47568

PCT/US00/02503

8

N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A·; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>†</sup>R<sup>9</sup>A·; -PR<sup>9</sup>-; -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A·; -P(O)R<sup>9</sup>-; radicals optionally may have one or more carbons replaced by -O-; -NR9-; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;

polypeptide residue; and phenylene; carbohydrate residue; amino acid residue; peptide residue; or wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

wherein M is a pharmaceutically acceptable cation; and

consisting of R9 and M; and

5 for the compounds of Formula I. wherein R9, R10, R11, R12, Rw, and A are as previously set forth above

More preferably, R3 or R6 has the formula -Ar-(R,),

t is an integer from 0 to 5;

2 pyridyl; piperazinyl; piperonyl; pyrrolyl; naphthyl; furanyl; anthracenyl; quinolinyl; isoquinolinyl; quinoxalinyl; imidazolyl; pyrazolyl; oxazolyl benzoimidazolyl; benzoxazolyl; benzothiazolyl; and benzoisothiazolyl; and isoxazolyl; pyrimidinyl; thiazolyl; triazolyl; isothiazolyl; indolyl; one or more RY are independently selected from the group consisting Ar is selected from the group consisting of phenyl; thiophenyl;

25 20 OM;  $-SO_2OM$ ;  $-SO_2NR^{13}R^{14}$ ;  $-C(O)NR^{13}R^{14}$ ; -C(O)OM;  $-COR^{13}$ ;  $-COR^{13}$ arylaikyi; heterocyclylaikyi; polyether; -OR13; -NR13R14; -SR13; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; NR"SO,NR"R"; -P(O)R 13R 14; -PR 13R 14; -P+R 13R 14R 15A; -NR13C(0)R14; -NR13C(0)NR14R15; -NR13CO2R14; -OC(0)R13; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OC(0)NR13R14; -NR13SOR14; -NR13SO,R14; -NR13SONR14R15; -

P(OR 13)OR 14; -S+R13R14A; and -N+R13R14R15A; and

may be further substituted with one or more radicals selected from the group  $\mathsf{heterocyclyl}; -\mathsf{OR}^7; -\mathsf{NR}^7 \mathsf{R}^8; -\mathsf{SR}^7; -\mathsf{S}(\mathsf{O}) \mathsf{R}^7; -\mathsf{SO}_2 \mathsf{R}^7; -\mathsf{SO}_3 \mathsf{R}^7; -\mathsf{CO}_2 \mathsf{R}^7; -\mathsf{SO}_3 \mathsf{R}^7$ heterocyclylalkyl, and polyether substituents of the RY radicals optionally wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, CONR 7R ; -N+R 7R 8R 4 .. -P(O)R 7R ; -PR 7R 8; -P+R 7R 8R 9A; and alkenyl, alkynyl, aryl, heterocyclyl, quatemary heterocyclyl, arylalkyl, consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quatemary

P(O)(OR7)OR8; and 2

may have one or more carbons replaced by -O-; -NR $^7$ -; -N $^+$ R $^8$ A--; -S-; heterocyclylalkyl, and polyether substituents of the RY radicals optionally SO:; -SO2:; -S<sup>+</sup>R<sup>7</sup>A:; -PR<sup>7</sup>:, -P(O)R<sup>7</sup>:, -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup>; or phenylene; and wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, 2

consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the wherein R7 and R8 are independently selected from the group

alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl;

wherein R13 and R14 together with the nitrogen atom to which they substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally oxo, carboxy, and quaternary salts; or

23

wherein  $R^{14}$  and  $R^{15}$  together with the nitrogen atom to which they

WO 00/47568

PCT/US00/02503

2

are attached form a cyclic ring; and

arylalkyl; heterocyciylalkyl; quatemary heterocyciylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; wherein the R 13, R 14, and R 15 alkyl; haloalkyl; cycloalkyl;

- ukylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected nydroxyalkyi; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;
- guanidinyl;  $-0R^{16}$ ;  $-NR^{9}R^{10}$ ;  $-N^{4}R^{9}R^{10}R^{W}A^{2}$ ;  $-SR^{16}$ ;  $-S(O)R^{9}$ ;  $-SO_{2}R^{9}$ ;  $PR^9R^{10}; -P^+R^9R^{10}R^{11}A$ -; -S $^+R^9R^{10}A$ -; and carbohydrate residue; and  $\text{SO}_{3}\text{R}^{16}$ ;  $\text{-CO}_{2}\text{R}^{16}$ ;  $\text{-CO}_{1}\text{R}^{9}$ ;  $\text{-PO}_{1}$ ;  $\text{$ wherein the R13, R14, and R15 alkyl; haloalkyl; cycloalkyl; heterocyclyl; quaternary heterocyclylalkyl; carboxy, carboxyalkyl; 2
  - ilkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O.; -NR9-; arylalkyi; heterocyclylalkyi; quatemary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; ulkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; 2
- 4<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; -5.; -50.; -50<sub>2</sub>; -5<sup>+</sup>R<sup>9</sup>A<sup>-</sup>; -PR<sup>9</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; -P(O)R<sup>9</sup>; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and 2

wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group consisting of R9 and M; and

wherein R, R1, R1, R1, R", and A are as previously set forth above wherein M is a pharmaceutically acceptable cation; and for the compounds of Formula I. 53

Still more preferably, at least one of R3 or R6 has the formula (II)

3

wherein RY and t are defined as above.

In the various embodiments of the invention, the compounds of Formula I preferably satisfy at least one or more of the following additional conditions:

S

 R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, alkyl and (C<sub>1,10</sub>)cycloalkyl. Preferably, R<sup>1</sup> and R<sup>2</sup> are

5

independently selected from the group consisting of hydrogen and  $(C_1, 0)$ alkyl. More preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of  $(C_{1,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of  $(C_{1,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of  $(C_{2,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are the same  $(C_{2,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are the same  $(C_{2,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are the same  $(C_{2,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are the same  $(C_{2,0})$ alkyl. Still more preferably,  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are the same  $(C_{2,0})$ alkyl.

5

(2) R³ and R⁴ are independently selected from the group consisting of hydrogen and -OR² wherein R³ is defined as previously set forth above for the compounds of Formula I. Preferably, R³ is hydrogen and R⁴ is -OR². Still more preferably, R³ is hydrogen and R⁴ is hydroxy. Still more preferably, the hydroxy group is in a syn relationship to the structure of

20

(3) R<sup>5</sup> is phenyl substituted with a radical selected from the group

WO 00/47568

consisting of -OR<sup>13</sup>, -NR<sup>13</sup>C(O)R<sup>14</sup>, -NR<sup>13</sup>C(O)NR<sup>14</sup>R<sup>13</sup>, -NR<sup>13</sup>CO<sub>2</sub>R<sup>14</sup>, -OC(O)RR<sup>13</sup>, -OC(O)NR<sup>13</sup>R<sup>14</sup>, -NR<sup>13</sup>SOR<sup>14</sup>, -NR<sup>13</sup>SO<sub>2</sub>R<sup>14</sup>, -NR<sup>13</sup>SONR<sup>14</sup>R<sup>13</sup>, and -NR<sup>13</sup>SO<sub>2</sub>NR<sup>14</sup>R<sup>13</sup> wherein R<sup>13</sup>, R<sup>14</sup> and R<sup>13</sup> are as previously set forth above for the compounds of Formula I. Still more preferably, R<sup>3</sup> is phenyl substituted with -OR<sup>13</sup> or -NR<sup>13</sup>C(O)R<sup>14</sup>. Still more preferably, R<sup>3</sup> is phenyl substituted at the para or meta position with -OR<sup>13</sup> wherein R<sup>13</sup> comprises a quaternary heterocyclyl, quaternary heterocyclylalkyl or alkylammoniumalkyl, or R<sup>3</sup> is phenyl substituted at the para or meta position with -NR<sup>13</sup>C(O)R<sup>14</sup> wherein R<sup>13</sup> is hydrogen and R<sup>14</sup> comprises a quaternary heterocyclyl, quaternary heterocyclylalkyl or alkylammoniumalkyl, and/or

(4) R6 is hydrogen; and/or

70

- (5) R<sup>N</sup> is selected from the group consisting of hydrogen, alkyl and aralkyl. Preferably, R<sup>N</sup> is selected from the group consisting of hydrogen,
  15 (C<sub>1-10</sub>)alkyl and aryl(C<sub>1-10</sub>)alkyl. More preferably, R<sup>N</sup> is selected from the group consisting of hydrogen, methyl, ethyl and benzyl. Still more preferably, R<sup>N</sup> is hydrogen; and/or
- (6) R<sup>4</sup> is independently selected from the group consisting of -QR<sup>13</sup>, -NR<sup>13</sup>R<sup>14</sup>, -NR<sup>13</sup>R<sup>14</sup>A, and polyether. More preferably, R<sup>2</sup> is selected
  from the group consisting of -QR<sup>13</sup> and -NR<sup>13</sup>R<sup>14</sup>. Still more preferably, R<sup>2</sup> is selected from the group consisting of alkoxy, amino, alkylamino and dialkylamino. Still more preferably, R<sup>2</sup> is selected from the group consisting of methoxy and dimethylamino; and/or
- (7) One or more R\* are present at the 7-, 8- or 9-position of the benzo
  25 ring of the structure of Formula I. Preferably, said R\* are present at the 7and 9-positions of the benzo ring of the structure of Formula I. More
  preferably, R\* is present at the 7-position of the benzo ring of the structure of
  Formula I; and/or
- (8) q is 1, 2 or 3. Preferably, q is 1 or 2, and more preferably q is 1;

23

and/or

(9) t is 1 or 2.

In still another embodiment of the invention, the compounds of Formula I satisfy at least one or more of the above-described conditions and

5 R<sup>3</sup> comprises a carbohydrate residue.

A more preferred class of compounds comprises those compounds of Formula I wherein:

q is an integer from 1 to 4;

 $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of

10 hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl; alkoxyalkynyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl; or

 $\rm R^1$  and  $\rm R^2$  taken together with the carbon to which they are attached form C\_3-C\_1\_0 cycloalkyl or C\_3-C\_1\_0 cycloalkenyl; and

- wherein the R<sup>1</sup> and R<sup>2</sup> alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl;
  alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl
  radicals optionally may be substituted with one or more radicals selected
  from the group consisting of -CN; halogen; oxo; -OR<sup>2</sup>; -NR<sup>9</sup>R<sup>10</sup>;

  N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup> A<sup>-</sup>; -SR<sup>9</sup>; -S<sup>\*</sup>R<sup>\*</sup>R<sup>10</sup>A<sup>-</sup>; -PR<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>-</sup>; -S(O)R<sup>9</sup>; SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; and -CONR<sup>9</sup>R<sup>10</sup>; and
  - alkoxyalkyl; alkoxyalkoyl; alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl; alkoxyalkynyl; alkoxyalkynyl; alkoxyalkyl)aryl radicals optionally may have one or more carbons replaced by -O-; -NR<sup>9</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; -S-: -SO-; -SO<sup>2</sup>; -S<sup>+</sup>R<sup>9</sup>A<sup>-</sup>-; -PR<sup>9</sup>-; -P(O)R<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>-; or phenylene; and
- wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>w</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alknyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl;

25

carboxyalkyl; carboalkoxyalkyl; carboxyheterocyclyl; carboxyalkylamino; and acyl; and

wherein A is a pharmaceutically acceptable anion; and

 $\mathbb{R}^3$  and  $\mathbb{R}^4$  are independently selected from the group consisting of

hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl;  $-OR_{9}^{9}$ ;  $-NR^{9}R^{10}$ ; . SR $^{9}$ ;  $-S(O)R^{9}$ ;  $-SO_{2}R^{9}$ ; and  $-SO_{3}R^{9}$ ; or  $R^{3}$ ; or  $R^{3}$  and  $R^{4}$  together form -O;  $=NOR^{9}$ ; =S;  $=NNR^{9}R^{10}$ ;  $=NNR^{9}R^{9}$ ; or

 $K^*$  and  $K^*$  together form =0; =NOR\*; =S; =NNR^R\*, =CR^{11}R^{12}.

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; carboxyalkyl; carboalkoxyalkyl; cycloalkyl; cyanoalkyl; -OR<sup>2</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; and -CONR<sup>9</sup>R<sup>10</sup>; or

 $R^{11}$  and  $R^{12}$  together with the carbon atom to which they are

attached form a cyclic ring; and

2

wherein R9 and R10 are as defined above; and

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>;

- wherein the R<sup>5</sup> and R<sup>6</sup> alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; cycloalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl;
  - 25 arylalkyl; heterocyclylalkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>CO<sub>3</sub>R<sup>14</sup>; -NR<sup>13</sup>CO<sub>3</sub>R<sup>14</sup>; -OC(O)R<sup>19</sup>; -OC(O)NR<sup>19</sup>R<sup>14</sup>; -NR<sup>13</sup>SO<sub>3</sub>R<sup>14</sup>; -NR<sup>13</sup>SO<sub>3</sub>R<sup>14</sup>

P(OR 13)OR 14; -S+R 13R 14A; and -N+R 13R 14R 15A; and NR"SO,NR"R"; -PR<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P<sup>†</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -

5 CONR7R8; -NTR7R8R9A-; -P(O)R7R8; -PR7R8; -PTR7R8R9A; and heterocyclylalkyl, and polyether substituents of the R' and R' radicals P(O)(OR')OR'; and heterocyclyl; -OR'; -NR'R's, -SR'; -S(O)R'; -SO2R'; -SO3R';- CO2R'; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; optionally may be further substituted with one or more radicals selected alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

 $N^{+}R^{7}R^{8}A^{-}$ ; -S-; -SO-; -SO2-; -S $^{+}R^{7}A^{-}$ ; -PR $^{7}$ ; -P(O)R $^{7}$ -; -P $^{+}R^{7}R^{8}A^{-}$ ; or optionally may have one or more carbons replaced by -O-; -NR'-; heterocyclylalkyl, and polyether substituents of the R<sup>5</sup> and R<sup>6</sup> radicals alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl

2

consisting of hydrogen and alkyl; and wherein  $R^7$  and  $R^8$  are independently selected from the group phenylene; and

20 alkylheterocyclylalkyl; alkylammoniumalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; wherein  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  are independently selected from the

23 carboxyalkylaminocarbonylalkyl; and polyether; or

are attached form a mono- or polycyclic heterocyclyl that is optionally oxo, carboxy, and quaternary salts; or substituted with one or more radicals selected from the group consisting of wherein R13 and R14 together with the nitrogen atom to which they

alkylarninocarbonylalkyl; carboxyalkylarninocarbonylalkyl; and polyether alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; from the group consisting of halogen; -CN; sulfo; oxo; alkyl; sulfoalkyl; radicals optionally may be substituted with one or more radicals selected are attached form a cyclic ring; and wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl;

wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they

5 SR<sup>16</sup>; -S(0)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; -CO<sub>N</sub>R<sup>9</sup>R<sup>10</sup>; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; SO2NR9R10; -PO(OR16)OR17; -PR9R10; -P+R9R10R11A; -S+R9R10A carboxy; carboxyalkyl; guanidinyl; -OR $^{16}$ , -NR $^{9}$ R $^{10}$ , -N $^{+}$ R $^{9}$ R $^{10}$ R $^{w}$ A $^{-}$ ; and carbohydrate residue; and

8 2 polypeptide residue; and phenylene; carbohydrate residue; amino acid residue; peptide residue; or  $N^{+}R^{9}R^{10}A :: -S: -SO: -SO: -SO_{::} -S^{+}R^{9}A :: -PR^{9}: -P^{+}R^{9}R^{10}A :: -P(O)R^{9}$ radicals optionally may have one or more carbons replaced by -O-; -NRº-; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether wherein the R  $^{13}$ , R  $^{14}$ , and R  $^{15}$  alkyl; haloalkyl; cycloalkyl;

25 consisting of R<sup>9</sup> and M; and wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

alkynyi; and aralkyi; and  $\mathbb{R}^N$  is selected from the group consisting of hydrogen; alkyl; alkenyl; wherein M is a pharmaceutically acceptable cation; and wherein R, R, R, R, R, R, and A are as defined above; and

wherein the R\* alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; radicals selected from the group consisting of halogen; -CN; oxo; -OR  $^{16}$ ; alkenyi; alkynyi; aryi; heterocyclyi; arylalkyi; heterocyclylalkyi; polyether; acyloxy radicals optionally may be further substituted with one or more  $\cos^{16}$ ; - $\cos^{9}$ R $^{10}$ ; - $\cos^{9}$ R $^{10}$ ; - $\cos^{9}$ R $^{10}$ ; - $\rm P^+R^9R^{11}R^{12}A^7$  ,  $\rm S^+R^9R^{10}A^7$  , and carbohydrate acid residue; and NR9R10; -N+R9R10RWAT; -SR16; -S(O)R9; -SO2R9; -SO3R16; 2

2

substituted with one or more radicals selected from the group consisting of wherein the R\* quaternary heterocyclyl radical optionally may be S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; and carbohydrate acid residue; and heterocyclylalkyl; polyether;  $-\mathrm{OR}^{13}$ ;  $-\mathrm{NR}^{13}\mathrm{R}^{14}$ ;  $-\mathrm{SR}^{13}$ ;  $-\mathrm{S}(\mathrm{O})\mathrm{R}^{13}$ ;  $-\mathrm{S}(\mathrm{O})\mathrm{R}^$ SO2R<sup>13</sup>; -SO3R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO2R<sup>13</sup>; OM;  ${
m SO}_2{
m OM}; {
m SO}_2{
m NR}^{13}{
m R}^{14}; {
m -C}({
m O}){
m NR}^{13}{
m R}^{14}; {
m -C}({
m O}){
m OM}; {
m -C}{
m OR}^{13};$ halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl;  $P(O)R^{13}R^{14}$ ;  $-PR^{13}R^{14}$ ;  $-P^+R^{13}R^{14}R^{15}A^*$ ;  $-P(OR^{13})OR^{14}$ ; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl;

23

2

or more carbons replaced by -O-; -NR  $^{13}$  ; -N  $^{+}\mathrm{R}^{13}\mathrm{R}^{14}\mathrm{A}$  -; -S-; -SO-; -SO2-; wherein the  $\mathbb{R}^{X}$  radicals comprising carbon optionally may have one -S+R<sup>13</sup>A-; -PR<sup>13</sup>; -P(O)R<sup>13</sup>; -PR<sup>13</sup>; -P+R<sup>13</sup>R<sup>14</sup>A-; phenylene; amino

PCT/US00/02503 WO 00/47568

polyalkyl optionally may have one or more carbons replaced by -0-; -NR  $^9$ -; acid; peptide; polypeptide; carbohydrate; polyether; or polyalkyl; wherein -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>:, -S.; -SO-; -S0<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A--; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A--; or said phenylene; amino acid; peptide; polypeptide; carbohydrate; and

P(0)R9-; and

wherein  $\mathbb{R}^{18}$  is selected from the group consisting of alkyl; alkenyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and alkynyl; aryi; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkoxycarbonyl; and

consisting of halogen; -CN; 0x0; -OR<sup>9</sup>; -NR<sup>9</sup>R <sup>10</sup>; -N<sup>+</sup>R<sup>9</sup>R <sup>11</sup>R <sup>12</sup>A<sup>-</sup>; -SR <sup>9</sup>; wherein the R13 alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may be substituted with one or more radicals selected from the group  $-s(0)R^9$ ;  $-so_2R^9$ ;  $-co_2R^9$ ;  $-coinr^9R^{10}$ ;  $-so_2oM$ ; heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; 2 2

 $SO_2NR^9R^{10}$ ;  $-PR^9R^{10}$ ;  $-P(OR^{13})OR^{14}$ ;  $-PO(OR^{16})OR^{17}$ ; and -C(O)OM;

defined above; or

A class of compounds of interest comprises those compounds of

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

2

q is an integer from 1 to 4;

Formula I wherein:

 $R^{\rm l}$  and  $R^{\rm 2}$  are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>3</sub>-C<sub>10</sub>)alkenyl; (C<sub>3</sub>-

- C<sub>10</sub>)alkynyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-22
- C10,3alkoxy(C2-C10,3alkeny); (C1-C10,3alkoxy(C2-C10,3alkyny); (C1-C10,alkylary); and (polyalkyl)aryl; or

form  $(C_3-C_{10})$ cycloalkyl; and  $\mathbb{R}^1$  and  $\mathbb{R}^2$  taken together with the carbon to which they are attached

PTRYR10RWA; -S(0)R9; -SO2R9; -SO3R9; -CO2R9; and -CONR9R10; oxo; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>w</sup>A<sup>-</sup>; -SR<sup>9</sup>; -S<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; -PR<sup>9</sup>R<sup>10</sup>; one or more radicals selected from the group consisting of -CN; halogen; C10) alkylaryl; and (polyalkyl) aryl radicals optionally may be substituted with  $(C_1-C_{10})$ alkoxy $(C_2-C_{10})$ alkenyl;  $(C_1-C_{10})$ alkoxy $(C_2-C_{10})$ alkynyl;  $(C_1-C_{10})$ alkoxy  $C_{10}$ )alkenyl; ( $C_2$ - $C_{10}$ )alkynyl; aryl( $C_1$ - $C_{10}$ )alkyl; ( $C_1$ - $C_{10}$ )alkoxy( $C_1$ - $C_{10}$ )alkyl; wherein the  $\mathbb{R}^1$  and  $\mathbb{R}^2$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>2</sub>

carbons replaced by -O-; -NR $^9$ -; -N $^+$ R $^9$ R $^{10}$ A--; -S-; -SO-; -SO<sub>2-</sub>; -S $^+$ R $^9$ A--; -PR $^9$ ; -P(O)R $^9$ -; -P $^+$ R $^9$ R $^{10}$ A $^-$ -; or phenylene; and  $C_{10}$ )alkylaryi; and (polyalkyl)aryi radicals optionally may have one or more  $(C_1-C_{10})$ alkoxy $(C_2-C_{10})$ alkenyl;  $(C_1-C_{10})$ alkoxy $(C_2-C_{10})$ alkynyl;  $(C_1-C_{10})$ alkoxy  $C_{10}$ )alkenyl;  $(C_2-C_{10})$ alkynyl; aryl $(C_1-C_{10})$ alkyl;  $(C_1-C_{10})$ alkoxy $(C_1-C_{10})$ alkyl; wherein the  $\mathbb{R}^1$  and  $\mathbb{R}^2$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>2</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>2</sub>-

consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>2</sub>-C<sub>10</sub>)eycloalkyl; (C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C2-C10)alkynyl; aryl; heterocyclyl; ammonium(C1-C10)alkyl; (C1wherein  $\mathbb{R}^9$ ,  $\mathbb{R}^{10}$ , and  $\mathbb{R}^w$  are independently selected from the group

20 C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>carboxyheterocyclyl; carboxy(C1-C10)alkylamino; and acyl; and  $C_{10}$ ) alkyl; carboxy( $C_1$ - $C_{10}$ ) alkyl; carbo( $C_1$ - $C_{10}$ ) alkoxy( $C_1$ - $C_{10}$ ) alkyl; wherein A is a pharmaceutically acceptable anion; and

hydrogen;  $(C_1-C_{10})$ alkyl;  $(C_2-C_{10})$ alkenyl;  $(C_2-C_{10})$ alkynyl; aryl; heterocyclyl;  $-OR^9$ ;  $-NR^9R^{10}$ ;  $-SR^9$ ;  $-S(O)R^9$ ;  $-SO_2R^9$ ; and  $-SO_3R^9$ ; or  $R^3$  and  $R^4$  together form =0; =NOR<sup>9</sup>; =S; =NNR<sup>9</sup>R<sup>10</sup>; =NR<sup>9</sup>; or  $R^3$  and  $R^4$  are independently selected from the group consisting of

25

wherein  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  are independently selected from the group

(C<sub>2</sub>-C<sub>10</sub>)alkynyl; aryl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; consisting of hydrogen; -CN; halogen; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>2</sub>-C<sub>10</sub>)alkenyl;

CONR<sup>9</sup>R<sup>10</sup>; or  $OR^9$ ;  $-NR^9R^{10}$ ;  $-SR^9$ ;  $-S(O)R^9$ ;  $-SO_2R^9$ ;  $-SO_3R^9$ ;  $-CO_2R^9$ ; and - ${\tt carbo}(C_1\text{-}C_{10}) \\ alkoxy(C_1\text{-}C_{10}) \\ alkyl; (C_3\text{-}C_{10}) \\ cycloalkyl; \\ cyano(C_1\text{-}C_{10}) \\ alkyl; \\ \cdot$ 

attached form a cyclic ring; and  ${
m R}^{11}$  and  ${
m R}^{12}$  together with the carbon atom to which they are

wherein R<sup>9</sup> and R <sup>10</sup> are as defined above; and

hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>2</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>2</sub>-S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; C<sub>10</sub>)alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR<sup>9</sup>; -SR<sup>9</sup>; - $\mathbb{R}^5$  and  $\mathbb{R}^6$  are independently selected from the group consisting of

5

5 C10) alkenyl; (C2-C10) alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; radicals optionally may be substituted with one or more radicals aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>, oxo;  $(C_1-C_{10})$ alkyl; polyalkyl; halo $(C_1-C_{10})$ alkyl;  $(C_3-C_{10})$ cycloalkyl;  $(C_2-C_{10})$ independently selected from the group consisting of halogen; -CN; -NO2;  $C_{10}$ ) alkenyl; ( $C_2$ - $C_{10}$ ) alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl wherein the  $R^5$  and  $R^6$  (C<sub>i</sub>-C<sub>i0</sub>)alkyl; (C<sub>j</sub>-C<sub>i0</sub>)cycloalkyl; (C<sub>j</sub>-

25 20 P(OR 13)OR 14; -S+R 13R 14A; and -N+R 13R 14R 15A; and COR 13; -NR 13C(O)R 14; -NR 13C(O)NR 14R 11; -NR 13CO,R 14; -OC(O)R 13; --SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>;  $CO_2R^{13}$ ; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR  $^{13}R^{14}$ ; -C(O)NR  $^{13}R^{14}$ ; -C(O)OM; OC(O)NR'3R'4; -NR'3SOR'4; -NR'3SO,R'4; -NR'3SONR'4R'5; -NR''3O,NR''R''; -P(O)R<sup>13</sup>R<sup>14</sup>; -PR<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -

C10) alkyl, and polyether substituents of the R3 and R6 radicals optionally  $C_{10}$ ) alkyl,  $(C_3$ - $C_{10}$ ) cycloalkyl,  $(C_2$ - $C_{10}$ ) alkenyl,  $(C_2$ - $C_{10}$ ) alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, aryl $(C_1-C_{10})$ alkyl, heterocyclyl $(C_1-C_{10})$ wherein the (C<sub>1</sub>-C<sub>10</sub>)alkyl, polyalkyl, halo(C<sub>1</sub>-C<sub>10</sub>)alkyl, hydroxy(C<sub>1</sub>-

may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl; -OR<sup>7</sup>; -NR<sup>7</sup>R<sup>8</sup>; -SR<sup>7</sup>; -(C2-C10)alkenyl; (C2-C10)alkynyl; aryl; heterocyclyl; aryl(C1-C10)alkyl;  $S(0)R^7$ ;  $-SO_2R^7$ ;  $-SO_3R^7$ ;  $-CO_2R^7$ ;  $-CONR^7R^8$ ;  $-N^{\dagger}R^7R^8R^9A_5$ ; -P(O)R  $^7\mathrm{R}^8;$  -PR  $^7\mathrm{R}^8;$  -P  $^+\mathrm{R}^7\mathrm{R}^8\mathrm{R}^9\mathrm{A}^*;$  and -P(O)(OR  $^7\mathrm{)OR}^8;$  and

wherein the (C1-C10)alkyl, polyalkyl, halo(C1-C10)alkyl, hydroxy(C1may have one or more carbons replaced by -O-; -NR<sup>7</sup>-; -N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>--</sup>; -S-; SO-; -SO2-; -S $^{+}R^{7}A$ -; -PR $^{7}$ -; -P(O)R $^{7}$ -; -P $^{+}R^{7}R^{8}A$ -; or phenylene; and heterocyclyl, quaternary heterocyclyl, aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl, heterocyclyl(C<sub>1</sub>-C10, alkyl, and polyether substituents of the R3 and R6 radicals optionally wherein  $\boldsymbol{R}^{7}$  and  $\boldsymbol{R}^{8}$  are independently selected from the group Cio)alkyl, (C3-Cio)cycloalkyl, (C3-Cio)alkenyl, (C3-Cio)alkynyl, aryl, consisting of hydrogen and (C1-C10)alkyl; and

2

heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>wherein  $R^{13},\,R^{14},\,$  and  $R^{15}$  are independently selected from the C<sub>10</sub>)alkyl; quatemary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl(C<sub>1</sub>group consisting of hydrogen; (C<sub>I</sub>-C<sub>10</sub>)alkyl; halo(C<sub>I</sub>-C<sub>10</sub>)alkyl; (C<sub>I</sub>-C<sub>10</sub>)cycloalkyl; polyalkyl; (C<sub>7</sub>-C<sub>10</sub>)alkenyl; (C<sub>7</sub>-C<sub>10</sub>)alkynyl; aryl; C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-2 2

 $C_{10}$ ) alky lammonium ( $C_1$ - $C_{10}$ ) alky  $J_1$ ; carboxy ( $C_1$ - $C_{10}$ ) alky lamino carbony  $J_1(C_1$ wherein R13 and R14 together with the nitrogen atom to which they C10) alkyl; and polyether; or

substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally oxo, carboxy, and quaternary salts; or 23

wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

wherein the R  $^1$ 3, R  $^1$ 4, and R  $^1$ 5 (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-

WO 00/47568

PCT/US00/02503

33

heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl (C<sub>1</sub>-C<sub>10</sub>)cycloalkyl; polyalkyl; (C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>2</sub>-C<sub>10</sub>)alkynyl; aryl; C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-

- oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; sulfo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl (C,-Cio)alkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-
- wherein the R 13, R 14, and R 15 (C1-C10)alkyl; halo(C1-C10)alkyl; (C3guanidinyl; -OR 16; -NR 9R 10; -N\*R 9R 10R WA; -SR 16; -S(O)R 9; -SO2R 9; PR9R10; -P+R9R10R11A-;-S+R9R10A-; and carbohydrate residue; and  $-so_3R^{16}$ ;  $-co_2R^{16}$ ;  $-conR^9R^{10}$ ;  $-so_2nR^9R^{10}$ ;  $-ro(oR^{16})oR^{17}$ ; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; 0
- heterocyclyi; quaternary heterocyclyi; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyi; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl(C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-Calcycloalkyl; polyalkyl; (C2-Calalkenyl; (C2-Calalkynyl; aryl; C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-2
- Cia)alkylaminocarbonyl(Ci-Cia)alkyl; and polyether radicals optionally may have one or more carbons replaced by -O.; -NRP.; -NTRPR 10A.; -S.; -SO.;  $\cdot SO_{2^*}; -S^+R^9A^* \cdot ; -PR^9 \cdot ; -P^+R^9R^{10}A^* \cdot ; -P(O)R^9 \cdot ; phenylene; carbohydrate$ residue; amino acid residue; peptide residue; or polypeptide residue; and C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-ឧ
- $\mathsf{R}^{\mathsf{N}}$  is selected from the group consisting of hydrogen; (  $\mathsf{C}_\mathsf{l}\text{-}\mathsf{C}_\mathsf{l0}$ )alkyl; wherein  $R^{\,16}$  and  $R^{\,17}$  are independently selected from the group wherein R, R10, R11, R12, R", and A are as defined above; and wherein M is a pharmaceutically acceptable cation; and consisting of R9 and M; and

23

 $(C_2-C_{10})$ alkenyl;  $(C_2-C_{10})$ alkynyl; and aryl $(C_1-C_{10})$ alkyl; and

 $C_{10}$ )cycloalkyl; polyalkyl; halo $(C_1-C_{10})$ alkyl;  $(C_2-C_{10})$ alkenyl;  $(C_3-C_{10})$ consisting of hydrogen; halogen; -CN; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>one or more RX radicals are independently selected from the group

polyether; acyloxy; -OR  $^{13}$ ; -NR  $^{13}\mathrm{R}^{14}$ ; -SR  $^{13}$ ; -S(O)R  $^{13}$ ; -S(O)R  $^{13}$ ; -C10)alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C1-C10)alkyl; COR<sup>13</sup>; -OR<sup>18</sup>; -S(O)nNR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>R<sup>18</sup>; -NR<sup>18</sup>OR<sup>14</sup>; -SO20M; -SO2NR  $^{13}$ R  $^{14}$ ; -NR  $^{14}$ C(O)R  $^{13}$ ; -C(O)NR  $^{13}$ R  $^{14}$ ; -C(O)OM; -SO3R<sup>13</sup>;-S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A;-NR<sup>13</sup>OR<sup>14</sup>;-NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>;-CO2R<sup>13</sup>;-OM;

acid residue; peptide acid residue; polypeptide acid residue; and N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -PR<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; amino carbohydrate acid residue;

5

heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; PR9R10; -P+R9R11R12A; or -S+R9R10A; and SO3R<sup>16</sup>; -CO2R<sup>16</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO2NR<sup>9</sup>R<sup>10</sup>; -PO(OR")OR";  $oxo; -OR^{16}; -NR^{9}R^{10}; -N^{+}R^{9}R^{11}R^{12}A^{-}; -SR^{16}; -S(O)R^{9}; -SO_{2}R^{9};$ acyloxy radicals optionally may be further substituted with halogen; -CN;  $C_{10}$ )alkyl; hydroxy( $C_1$ - $C_{10}$ )alkyl; ( $C_2$ - $C_{10}$ )alkenyl; ( $C_2$ - $C_{10}$ )alkynyl; aryl; wherein the  $\mathbb{R}^*$  ( $C_i$ - $C_{10}$ )alkyl; ( $C_j$ - $C_{10}$ )cycloalkyl; polyalkyl; halo( $C_i$ 

2

 $OR^{13}$ ;  $-NR^{13}R^{14}$ ;  $-SR^{13}$ ;  $-S(O)R^{13}$ ;  $-SO_2R^{13}$ ;  $-SO_3R^{13}$ ;  $-NR^{13}OR^{14}$ ; P+R13R14R15A;-P(OR13)OR14;-S+R13R14A; and-N+R13R14R15A; C(0)NR<sup>13</sup>R<sup>14</sup>; -C(0)OM; -COR<sup>13</sup>; -P(0)R<sup>13</sup>R<sup>14</sup>; -PR<sup>13</sup>R<sup>14</sup>;  $NR^{13}NR^{14}R^{15}$ ; -CO2R 13; -OM; -SO2OM; -SO2NR 13R 14; aryl; heterocyclyl; aryl(C1-C10)alkyl; heterocyclyl(C1-C10)alkyl; polyether;  $halo(C_i-C_{i0})alkyl;\ hydroxy(C_i-C_{i0})alkyl;\ (C_2-C_{i0})alkenyl;\ (C_3-C_{i0})alkynyl;$ halogen; -CN; -NO2; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; polyalkyl; substituted with one or more radicals selected from the group consisting of wherein the R\* quaternary heterocyclyl radical optionally may be

25

20

PCT/US00/02503

WO 00/47568

4

-S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>-; -PR<sup>13</sup>-; -P(O)R<sup>13</sup>-; -PR<sup>13</sup>-; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>-; phenylene; amino or more carbons replaced by -O-; -NR<sup>13</sup>-; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A-; -S-; -SO-; -SO<sub>2</sub>-; acid residue; peptide residue; polypeptide residue; carbohydrate residue; wherein the RX radicals comprising carbon optionally may have one

SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; or -P(O)R<sup>9</sup>-; and may have one or more carbons replaced by -O-; -NR -; -N+R R A -; -S-; residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide

C<sub>10</sub>)alkoxycarbonyl; and heterocyclyl; quaternary heterocyclyl; aryl(C1-C10)alkyl; acyl; and aryl(C1wherein  $R^{18}$  is selected from the group consisting of  $(C_i-C_{i0})$ alkyl;

5

consisting of halogen; -CN; oxo; -OR9; -NR9R10; -N+R9R11R12A-; -SR9; SO2NR<sup>9</sup>R<sup>10</sup>; -PR<sup>9</sup>R<sup>10</sup>; -P(OR<sup>13</sup>)OR<sup>14</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; and -C(O)OM;  $-S(O)R^{9}; -SO_{2}R^{9}; -SO_{3}R^{9}; -CO_{2}R^{9}; -CO_{1}R^{9}R^{10}; -SO_{2}OM;$ may be substituted with one or more radicals selected from the group aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; acyl; and aryl(C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl radicals optionally wherein the R16 (C1-C10)alkyl; heterocyclyl; quaternary heterocyclyl;

ᅜ

defined above; or wherein R?, R10, R11, R12, R13, R14, R15, R16, R17, Rw, A, and M are as

20

substituted phenyl, biphenyl and naphthyl; and provided that aryl is selected from the group consisting of optionally a pharmaceutically acceptable salt, solvate, or prodrug thereof, and

23 group consisting of oxygen, nitrogen, sulfur and phosphorus. optionally substituted heterocyclyl comprising a 5 to 10 membered ring and comprising one or more ring atoms that are heteroatoms selected from the provided that heterocyclyl is selected from the group consisting of

A class of compounds of particular interest comprises those

PCT/US00/02503

35

compounds of Formula I wherein:

q is an integer from 1 to 4;

 $\rm R^1$  and  $\rm R^2$  are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl,

- teri-butyl, pentyl, hexyl, phenoxymethylene, phenoxypthylene, phenoxypropylene, pyridinyloxymethylene, pyridinyloxyethylene; methylpyridinyloxymethylene, methylpyridinyloxyethylene, pyrimidinyloxymethylene, and pyrimidinyloxyethylene; or
- R<sup>1</sup> and R<sup>2</sup> taken together with the carbon to which they are attached form cyclopropyl, cyclobutyl, cyclopentyl, or cyclobexyl; and

2

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, phenyl, pyridinyl, amino, methylamino, dimethylamino, ethylamino and diethylamino; and

 $\mathbb{R}^5$  and  $\mathbb{R}^4$  are independently selected from the group consisting of

- hydrogen, phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, hydroxyphenyl, methoxyphenyl, ethoxyphenyl, methoxy(chlorophenyl), methoxy(fluorophenyl), methoxy(chlorophenyl), ethoxy(chlorophenyl), ethoxy(chlorophenyl), ethoxy(iodophenyl), nitrophenyl), aminophenyl, methylaminophenyl,
  - 20 dimethylaminophenyl, ethylaminophenyl, diethylaminophenyl, trimethylammoniumphenyl, triethylammoniumphenyl, trimethylammoniummethylcarbonylaminophenyl, triethylammoniummethylcarbonylaminophenyl, triethylammoniummethylcarbonylaminophenyl, trimethylammoniumethylcarbonylaminophenyl,
- 15 triethylammoniumethylcarbonylaminophenyl, trimethylammoniumpropylcarbonylaminophenyl, triethylammoniumpropylcarbonylaminophenyl, trimethylammoniumbutylcarbonylaminophenyl, triethylammoniumbutylcarbonylaminophenyl, methylcarbonylaminophenyl

WO 00/47568

PCT/US00/02503

36

chloromethylcarbonylaminophenyl, fluoromethylcarbonylaminophenyl, bromomethylcarbonylaminophenyl, iodomethylcarbonylaminophenyl, ethylcarbonylaminophenyl, chloroethylcarbonylaminophenyl, folloroethylcarbonylaminophenyl, hromoethylcarbonylaminophenyl,

- iodoethylcarbonylaminophenyl, propylcarbonylaminophenyl, chloropropylcarbonylaminophenyl, fluoropropylcarbonylaminophenyl, bromopropylcarbonylaminophenyl, iodopropylcarbonylaminophenyl, butylcarbonylaminophenyl, chlorobutylcarbonylaminophenyl, fluorobutylcarbonylaminophenyl, bromobutylcarbonylaminophenyl,
- 10 iodobutylcarbonylaminophenyl, 3,4-dioxymethylenephenyl, pyridinyl, methylpyridinyl, pyridinium, methylpyridinium, thienyl, chlorothienyl, fluorothienyl, bromothienyl, iodothienyl; methoxycarbonylphenyl, ethoxycarbonylphenyl, trimethylammoniumethoxyethoxyethoxyphenyl, triethylammoniumethoxyethoxyethoxyphenyl,
- chloroethoxyethoxyphenyl, fluoroethoxyethoxyphenyl, bromoethoxyethoxypthenyl, iodoethoxyethoxypthenyl, pyridiniumethoxyethoxypthenyl, piperazinyloxymethoxyethoxyphenyl,
- methylpiperazinyloxymethoxyethoxyethoxyphenyl,
  dimethylpiperazinyloxymethoxyethoxyethoxyphenyl,
  piperidinyloxymethoxyethoxyphenyl,
  methylpiperidinyloxymethoxyethoxyethoxyphenyl, and
  dimethylpiperidinyloxymethoxyethoxyethoxyphenyl, and

2

R<sup>N</sup> is selected from the group consisting of hydrogen, methyl, ethyl,

22

n-propyl, n-butyl, n-pentyl, n-hexyl and benzyl; and one or more R<sup>X</sup> radicals are independently selected from the group consisting of hydroxy, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, methylthio, methylsulfinyl, ethylthio, ethylsulfinyl, ethylsulfinyl, ethylsulfinyl, ethylsulfinyl,

methylcarbonylamino, chloromethylcarbonylamino, carboxymethyl-amino, N,N-dimethyl-N-carboxymethyl-ammonium, diethylamino, trimethylammonium, triethylammonium, N-methyl-Namino, hydroxyamino, methylamino, dimethylamino, ethylamino,

5 methyl-pyrrolidinium, piperazinyl, N-methylpiperazinyl, N,N'-dimethylpiperazinium, piperidinyl, methylpiperidinyl, N-methyl-piperidinium, and methyl-morpholinium, azetidinyl, N-methyl-azetidinium, pyrrolidine, Nbenzyloxycarbonylamino, aminoimidocarbonylamino, morpholinyl, Nbutylcarbonylamino, n-pentylcarbonylamino, n-hexylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, nfluoromethylcarbonylamino, bromomethylcarbonylamino,

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

A class of compounds of specific interest comprises those

q is an integer from 1 to 4;

15

compounds of Formula I wherein:

hydrogen and (C<sub>1</sub>-C<sub>10</sub>)alkyl; or  $\mathbb{R}^{1}$  and  $\mathbb{R}^{2}$  are independently selected from the group consisting of

form (C3-C10)cycloalkyl; and  $\mathbb{R}^1$  and  $\mathbb{R}^2$  taken together with the carbon to which they are attached

20

hydrogen and hydroxy; and  ${
m R}^3$  and  ${
m R}^4$  are independently selected from the group consisting of

heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; and -NR <sup>13</sup>C(O)R <sup>14</sup>;  $halogen; \ hydroxy; -NO2; \ (C_i-C_{10})alkyl; \ halo(C_i-C_{10})alkyl; \ aryl(C_i-C_{10})alkyl; \ halo(C_i-C_{10})alkyl; \ halo(C_i-C_{10})alky$ or more radicals independently selected from the group consisting of  $\mathbb{R}^2$  is phenyl, wherein said phenyl is optionally substituted with one

25

wherein  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  are independently selected from the

 $C_{10}$ )alkyl;  $(C_1-C_{10})$ alkylammonium $(C_1-C_{10})$ alkyl; and polyether; or quaternary heterocyclyi(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyi(C<sub>1</sub>quaternary heterocyclyl; aryl( $C_1$ - $C_{10}$ )alkyl; heterocyclyl( $C_1$ - $C_{10}$ )alkyl; group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl;

 $C_{10}) alkylheterocyclyl(C_1-C_{10}) alkyl; (C_1-C_{10}) alkylammonium (C_1-C_{10}) alkyl; (C_1-C_{10}) alkylight (C_1-C_1) alkylight (C_1-C_1)$ C10)alkyl; quaternary heterocyclyl(C1-C10)alkyl; (C1heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>wherein the R  $^{13}$ , R  $^{14}$ , and R  $^{15}$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl;

carboxy; carboxy(C;-C;0)alkyl; -OR  $^{16};$  -NR  $^9R\,^{10};$  -N  $^+R\,^9R\,^{10}R^WA^-;$  and radicals selected from the group consisting of halogen; (C,-C10)alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl $(C_1-C_{10})$ alkyl; and polyether radicals optionally may be substituted with one or more

5

2 consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C10)alkyl; carboxyheterocyclyl; carboxy(C1-C10)alkylamino; and acyl; or  $heterocyclyl(C_1-C_{10})alkyl;\ carboxy(C_1-C_{10})alkyl;\ carbo(C_1-C_{10})alkoxy(C_1-C_{10})alkoxy(C_1-C_{10})alkoxy(C_1-C_{10})alkoxy(C_1-C_{10})alkyl;\ carboxy(C_1-C_{10})alkyl;\ carboxy(C_1-C_{10})alkyl;$  $C_{10}) alkyl; (C_1 - C_{10}) alkylammonium (C_1 - C_{10}) alkyl; aryl (C_1 - C_{10}) alkyl;$ wherein A is a pharmaceutically acceptable anion; and wherein  ${
m R}^9$  and  ${
m R}^{10}$  are independently selected from the group

20  $carboxy(C_{i}\text{-}C_{10})alkyl; \ and \ carbo(C_{i}\text{-}C_{10})alkoxy(C_{i}\text{-}C_{10})alkyl; \ or \ although \ and \ carboxy(C_{i}\text{-}C_{i0})alkyl; \ or \ although \ and \ although \ and \ although \ although \ although \ and \ although \ although \ and \ although \ although$ consisting of hydrogen; (C1-C10)alkyl; heterocyclyl; aryl(C1-C10)alkyl; attached form a cyclic ring; and  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  together with the carbon atom to which they are wherein  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  are independently selected from the group

25 compounds of Formula I; and wherein R" and R16 are as previously set forth above for the

R6 is hydrogen; and

and aryl(C1-C10)alkyl; and  $\mathbb{R}^N$  is selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl;

PCT/US00/02503

30

one or more  $R^X$  radicals are independently selected from the group consisting of hydrogen; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>;

wherein R13 and R14 are as defined above; or

a pharmaceutically acceptable sait, solvate, or prodrug thereof; and provided that aryl is selected from the group consisting of optionally substituted phenyl, biphenyl and naphthyl; and

provided that heterocyclyl is selected from the group consisting of optionally substituted heterocyclyl comprising a 5 to 10 membered ring and comprising one or more ring atoms that are heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus.

2

A class of compounds of high interest comprises those compounds of Formula 1 wherein:

q is an integer from 1 to 4;

15  $$\rm R^1\,and\,R^2$  are independently selected from the group consisting of ethyl and n-butyl; or

 $\mathbb{R}^1$  and  $\mathbb{R}^2$  taken together with the carbon to which they are attached form cyclopentyl; and

one of  $\mathbb{R}^3$  and  $\mathbb{R}^4$  is hydrogen and the other of  $\,\mathbb{R}^3$  and  $\,\mathbb{R}^4$  is

20 hydroxy; and

R<sup>5</sup> is selected from the group consisting of phenyl, hydroxyphenyl, methoxyphenyl, ethoxyphenyl, nitrophenyl, aminophenyl, methylaminophenyl, dimethylaminophenyl, ethylaminophenyl, diethylaminophenyl, trinethylammoniumphenyl, triethylammoniumphenyl,

25 trimethylammoniummethylcarbonylaminophenyl, triethylammoniummethylcarbonylaminophenyl, trimethylammoniumethylcarbonylaminophenyl, triethylammoniumethylcarbonylaminophenyl,

WO 00/47568 PCT/US00/02503

40

trimethylammoniumpropylcarbonylaminophenyl, triethylammoniumpropylcarbonylaminophenyl, trimethylammoniumbutylcarbonylaminophenyl, triethylammoniumbutylcarbonylaminophenyl, methylcarbonylaminophenyl,

- chloromethylcarbonylaminophenyl, fluoromethylcarbonylaminophenyl, bromomethylcarbonylaminophenyl, iodomethylcarbonylaminophenyl, ethylcarbonylaminophenyl, ethylcarbonylaminophenyl, fluoroethylcarbonylaminophenyl, fluoroethylcarbonylaminophenyl, iodoethylcarbonylaminophenyl, propylcarbonylaminophenyl, iodoethylcarbonylaminophenyl,
- 10 chloropropylcarbonylaminophenyl, fluoropropylcarbonylaminophenyl, bromopropylcarbonylaminophenyl, iodopropylcarbonylaminophenyl, butylcarbonylaminophenyl, chlorobutylcarbonylaminophenyl, fluorobutylcarbonylaminophenyl, bromobutylcarbonylaminophenyl, iodobutylcarbonylaminophenyl,
- trimethylammoniumethoxyethoxyethoxyphenyl,
  triethylammoniumethoxyethoxyethoxyphenyl,
  chloroethoxyethoxyphenyl, fluoroethoxyethoxyphenyl,
  bromoethoxyethoxyphenyl, iodoethoxyethoxyphenyl, and
  pyridiniumethoxyethoxyphenyl; and

2

20 R<sup>6</sup> is hydrogen;

 $\mathbb{R}^{N}$  is selected from the group consisting of hydrogen, methyl, ethyl, and benzyl; and

one or more  $R^X$  radicals are independently selected from the group consisting of hydroxy, methyl, ethyl, methoxy, ethoxy, amino,

25 hydroxyamino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium, N-methyl-N-carboxymethyl-amino, R)N-dimethyl-N-carboxymethyl-ammonium, methylcarbonylamino, chloromethylcarbonylamino, fluoromethylcarbonylamino, bromomethylcarbonylamino, iodomethylcarbonylamino,

ethylcarbonylamino, benzyloxycarbonylamino, and aminoimidocarbonylamino; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

compounds of Formula I wherein: A subclass of compounds of high interest comprises those

wherein:

q is 1 or 2;

R and R2 are each independently alkyl;

R<sup>3</sup> is hydroxy;

R<sup>5</sup> has the formula (II): R<sup>4</sup> and R<sup>6</sup> are hydrogen;

wherein t is an integer from 0 to 5;

of hydrogen; halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; one or more RY are independently selected from the group consisting

2 hydroxyalkyi; cycloalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>C(O)NR<sup>14</sup>R<sup>15</sup>; -NR<sup>13</sup>CO,R<sup>14</sup>; -OC(O)R<sup>15</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; - $CO_2R^{13}$ ; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR 13; -NR 13R 14;

NR"SO,NR"R"; -P(O)R 13R 14; -PR 13R 14; -P+R 13R 14R 15A; OC(O)NR"R"; -NR"SOR"; -NR"SO,R"; -NR"SONR"R"; -P(OR 13)OR 14; -S+R 13R 14A; and -N+R 13R 14R 15A; and

20

consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; P(O)(OR )OR8; and heterocyclyl;  $-OR^7$ ;  $-NR^7R^8$ ;  $-SR^7$ ;  $-S(O)R^7$ ;  $-SO_2R^7$ ;  $-SO_3R^7$ ;  $-CO_2R^7$ may be further substituted with one or more radicals selected from the group CONR 7R8; -N+R7R8R9A-; -P(O)R7R8; -PR7R8; -P+R7R8R9A; and alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl, and polyether substituents of the RY radicals optionally alkenyl, alkynyl, aryl, heterocyclyl, quatemary heterocyclyl, arylalkyl, wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

20 15 5 alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; SO-; -SO2-; -S<sup>+</sup>R<sup>7</sup>A-; -PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-; or phenylene; and may have one or more carbons replaced by -O-; -NR $^7$ -; -N $^+$ R $^7$ R $^8$ A-; -S-; heterocyclylalkyl, and polyether substituents of the RY radicals optionally alkenyi, alkynyi, aryi, heterocyclyi, quaternary heterocyclyi, aryialkyi, alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the

23 are attached form a mono- or polycyclic heterocyclyl that is optionally are attached form a cyclic ring; and oxo, carboxy, and quaternary salts; or substituted with one or more radicals selected from the group consisting of wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they wherein R13 and R14 together with the nitrogen atom to which they

PCT/US00/02503

43

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyl; haloalkyl; cycloalkyl; polyalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylarmoniumalkyl; aminocarbonylalkyl;

- alkylaminocarbonylalkyi, carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR<sup>16</sup>, -NR<sup>9</sup>R<sup>10</sup>, -N<sup>4</sup>R<sup>9</sup>R<sup>10</sup>RW<sup>A</sup>; -SR<sup>16</sup>, -S(O)R<sup>9</sup>, -SO<sub>2</sub>R<sup>9</sup>, -SO<sub>3</sub>R<sup>16</sup>, -CO<sub>2</sub>R<sup>16</sup>, -CONR<sup>9</sup>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, -PO(OR<sup>16</sup>)OR<sup>17</sup>, -PR<sup>9</sup>R<sup>10</sup>, -P\*R<sup>9</sup>R<sup>10</sup>, -A\*R<sup>9</sup>R<sup>10</sup>, -A\*R<sup>10</sup>, -A\*R<sup>10</sup>
  - guanidinyi; -OR<sup>10</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>4</sup>R<sup>9</sup>R<sup>10</sup>R<sup>w</sup>A; -SR<sup>16</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>;
     -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>;
     PR<sup>9</sup>R<sup>10</sup>; -P<sup>4</sup>R<sup>9</sup>R<sup>10</sup>R<sup>11</sup>A-; -S<sup>4</sup>R<sup>9</sup>R<sup>10</sup>A-; and carbohydrate residue; and wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyl; haloalkyl; cycloalkyl;
     polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl;
     arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl;
    - arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O.; -NR<sup>9</sup>.; -N<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A·; -S.; -SO·; -SO·; -S<sup>+</sup>R<sup>9</sup>A·; -PR<sup>9</sup>; -P<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A·; -P(O)R<sup>9</sup>.;
- 20 phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and wherein  $R^{16}$  and  $R^{17}$  are independently selected from the group consisting of  $R^9$  and M; and

wherein M is a pharmaceutically acceptable cation; and

wherein R', R'', R'', R'', R'', and A are as previously set forth above for the compounds of Formula I; and

 $\mathbb{R}^N$  is selected from the group consisting of hydrogen; alkyl; and aralkyl; and

one or more RX radicals are independently selected from the group

WO 00/47568

PCT/US00/02503

77

consisting of alkoxy, alkylamino and dialkylamino; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

A family of specific compounds of particular interest within Formula I consists of the following compounds:

5 (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-1,2-benzothiazzepin-4-ol 1,1-dioxide;

10 S-chloro-N-[3-[(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazzepin-5-yl]phenyl]pentanamide; 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N.N.N-triethyl-5-oxo-pentanaminium trifluoroacetate;

15 2-chloro-N-[3-[(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]acetamide;

2-[[3-[[4R,5R]-3,3-dibutyl-7-(dimethylamino]-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-2-oxoethanaminium chloride;

2

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;

hydroxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-(((2iodoethyoxy)ethoxy)ethoxy)phenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-

hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5yl]phenoxy]ethoxy]ethyl]pyridinium; 1-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-

ಕ 2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4yl]phenoxy]ethoxy]-N,N,N-triethylethanaminium iodide; hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-

methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-

5

(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,2-benzothiazepin-4-ol 1,1-dioxide and (45,5R)-3,3-dibuty1-7-(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-

(4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,2-benzothiazepin-4-ol 1,1-dioxide;

20

hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl)phenyl]pentanamide; 5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-

8

pentanaminium trifluoroacetate; 1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-1-5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-phenyl-1,2-

benzothiazepin-4-ol 1,1-dioxide;

methoxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

hydroxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

<del>5</del> hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]-N,N,N-2-[2-[4-[(4R,5R)-3,3-dibutyl-7- (dimethylamino)-2,3,4,5-tetrahydro-4triethylethanaminium iodide;

(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2-

5

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-5-[3-(ethylamino)phenyl]-2,3,4,5tetrahydro-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4methoxyphenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; and

20 spiro[1,2-benzothiazepine-3(2H),1'-cyclopentan]-4-ol 1,1-dioxide; and (4R,5R)-7-dimethylamino)-2-ethyl-4,5-dihydro-5-(4-methoxyphenyl)-

the pharmaceutically-acceptably salts thereof.

The invention further comprises a compound selected from among:

2

wherein R<sup>19</sup> is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate residue, amino acid residue, peptide residue, and polypeptide residue; and

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy

diyl, polyether diyl, polyalkoxy diyl, carbohydrate residue, amino acid residue,
peptide residue, and polypeptide residue optionally may have one or more
carbon atoms replaced by -O., -NR², -N'R?R⁴A-, -S-, -SO-, -SO<sub>2</sub>, -S\*R²A-,
PR²-, -PR²R⁴A-, phenylene, heterocyclyl, quaternary heterocyclyl, or aryl;
wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy

15 diyl, polyether diyl, polyalkoxy diyl, carbohydrate residue, amino acid residue, peptide residue, and polypeptide residue optimally can be substituted with one

WO 00/47568

PCT/US00/02503

40

 wherein  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , M and  $A^{c}$  are as previously set forth above for the compounds of Formula I; and

wherein R<sup>19</sup> can further comprise functional linkages by which R<sup>19</sup> is bonded to R<sup>20</sup> and/or R<sup>21</sup> in the compounds of Formula DI; to R<sup>20</sup>, R<sup>21</sup> and/or R<sup>21</sup> in the compounds of Formula DII; and to R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup> and/or R<sup>23</sup> in the compounds of Formula DIII; and

wherein each of R<sup>20</sup>, R<sup>21</sup>, or R<sup>22</sup> and R<sup>21</sup> comprises a benzothiazepine 15 moiety as described above that is therapeutically effective in inhibiting iteal bile acid transport.

Exemplary R's substituents include, but are not limited to, the

S

49

· R<sup>25</sup> is selected from the group consisting of carbon and nitrogen; and R16, R27, R21, R29, R10, R31, R32, R31, R34, R31, R34, and R37 are

independently selected from the group consisting of:

and heterocyclylalkyl; consisting of alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocyclyl, wherein  $R^{38}$  ,  $R^{39},\,R^{40}$  and  $R^{41}$  are independently selected from the group

A' is a pharmaceutically acceptable anion; and

integers from 1 to 10 inclusive. h, i, j and k are independently selected from the group consisting of

PCT/US00/02503

2

The invention is also directed to a compound selected from among Formula DI, Formula DII and Formula DIII in which each of  $R^{2}$ ,  $R^{1}$ ,  $R^{2}$  and  $R^{2}$  comprises a benzothiazepine moiety corresponding to the Formula DIV or Formula DIVA:

-

wherein R', R', R', R', R', R', R', R', q, and n are as previously defined above for the compounds of Formula I, and R''s is either a covalent bond or arylene.

WO 00/47568

PCT/US00/02503

•

In compounds of Formula DIV, it is particularly preferred that each of R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, and R<sup>23</sup> in Formulae DI, DII and DIII be bonded at its 7- or 8-position to R<sup>19</sup>. In compounds of Formula DIVA, it is particularly preferred that R<sup>15</sup> comprise a phenylene moiety bonded at a m- or p-carbon thereof to R<sup>19</sup>.

Examples of Formula DI include:

and

gug

54

S

3

among other combinations, ethyl/butyl or butyl/butyl. definitions as stated above for R1, R2, R3, R4, R1, R2, R3, q and t, respectively. In any of the compounds of the present invention, R1 and R2 can be, Illustrative dimeric compounds include the following: wherein R14, R24, R34, R44, RN4, Ry4, RX4, r and u have the same

In another embodiment, a core moiety backbone, R<sup>19</sup>, as discussed herein in Formulae DI, DII and DIII can be multiply substituted with more than four pendant active benzothiazepine units, i.e., R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, and R<sup>23</sup> as discussed above, through multiple functional groups within the core moiety backbone. The core moiety backbone unit, R<sup>19</sup>, can comprise a single core moiety unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, i.e., alone or in combination. The number of individual core moiety backbone units can range from about one to about 100, preferably about one to about 50, and

attachment of similar or different pendant active benzothiazepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. Such points of attachment can include bonds to C, S, O, N, or P within any of the groups encompassed by the definition of R!?

The more preferred benzothiazepine moieties comprising R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup> and/or R<sup>21</sup> conform to the preferred structures as outlined above for Formula I. The 3-position carbon on each benzothiazepine moiety can be achiral, and the substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>2</sup> can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(oxyalkylene) or oligo(oxyalkylene), especially poly- or oligo(oxyalkylene).

ន

#### Methods of Treatment

23

In another aspect, the present invention provides a pharmaceutical composition for the prophylaxis and/or treatment of a disease, condition and/or disorder for which a bile acid transport inhibitor is indicated, such as a hyperlipidemic condition, for example, atherosclerosis. Such compositions

WO 00/47568

PCT/US00/02503

\*

comprise any of the compounds disclosed above, alone or in combination, in an amount effective to reduce bile acid levels in the blood, or to reduce transport thereof across digestive system membranes, alone or in a composition comprising, for example, one or more pharmaceutically acceptable carriers,

excipients, and/or diluents. In any of the dimeric or multimeric structures discussed immediately above, for example, the benzothiazepine compounds of the present invention can be used alone or in various combinations.

In a further aspect, the present invention also provides a method of treating a disease, condition and/or disorder in mammals, including humans, for which a bile acid transport inhibitor is indicated, comprising administering to a patient in need thereof a compound of the present invention in an effective

2

amount in unit dosage form or in divided doses.

In yet a further aspect, the present invention comprises the use of the compounds of Formula I and/or the dimeric or multimeric compounds of Formulae DI, DII and/or DIII in the preparation of a medicament useful for the prophylaxis and/or treatment of a disease, condition and/or disorder for which a bite acid transport inhibitor is indicated.

2

The compounds of Formula I are also useful for the prophylaxis and/or treatment of gallstones.

20 In yet a further aspect, the present invention also provides processes for the preparation of compounds of the present invention. Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while

indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

## Definitions and Abbreviations

9

alkenaryl and alkynaryl. Preferably, these moieties comprise 1 to 20 carbon substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, also include alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties. These radicals elements carbon and hydrogen. These radicals include, for example, alkyl, The term "hydrocarbyl" refers to radicals consisting exclusively of the

20 5 2 chain atom is replaced with a heteroatom such as nitrogen, oxygen, sulfur, or Substituted hydrocarbyl also includes hydrocarbyl radicals in which a carbon hydroxy; protected hydroxy; acyl; acyloxy; nitro; cyano; amino; and amido. acetals; ketals; esters, heterocyclyl such as furyl and thienyl; alkanoxy; methoxy, ethoxy, and butoxy; halogen such as chloro and fluoro; ethers; substituted with groups such as, but not limited to, lower alkoxy such as Examples of such substituted hydrocarbyl include hydrocarbyl radicals as but not limited to, halogen, oxygen, nitrogen, sulfur and phosphorus. is substituted with a group comprising at least one atom other than carbon, such The term "substituted hydrocarbyl" refers to a hydrocarbyl radical that

one to about six carbon atoms. Examples of such radicals include methyl, ethyl; n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoone to three carbon atoms amyl, hexyl and the like. Even more preferred are lower alkyl radicals having carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having having one to about twenty carbon atoms or, preferably, one to about twelve as "haloalkyl", and "hydroxyalkyl", it embraces linear or branched radicals Where the term "alkyl" is used, either alone or within other terms such

25

such as "arylalkenyl", it embraces linear or branched radicals having at least Where the term "alkeny!" is used, either alone or within other terms

೪

WO 00/47568 PCT/US00/02503

58

methylbutenyl. of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4are "lower alkenyl" radicals having two to about six carbon atoms. Examples preferably, two to about twelve carbon atoms. More preferred alkenyl radicals one carbon-carbon double bond of two to about twenty carbon atoms or,

and "trans" orientations, or alternatively, "B" and "Z" orientations. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis' S

to about six carbon atoms. Examples of such radicals include propargyl, More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two butynyl, and the like. about twenty carbon atoms or, preferably, two to about twelve carbon atoms The term "alkynyl" denotes linear or branched radicals having two to

5

8 2 three to about twelve carbon atoms. More preferred cycloalkyl radicals are heterocyclic ring of the benzothiazepine. cycloalkyl ring has a carbon ring atom in common with the seven-membered The term "cycloalkyl" additionally encompasses spiro systems wherein the of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. "lower cycloalkyl" radicals having three to about ten carbon atoms. Examples The term "cycloalkyl" embraces saturated carbocyclic radicals having

cyclopentenyl and cyclohexenyl. preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to partially unsaturated carbocyclic radicals that contain two double bonds (that about ten carbon atoms. Examples of such radicals include cyclobutenyl, may or may not be conjugated) can be called "cycloalkyldienyl". More radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are The term "cycloalkenyl" embraces partially unsaturated carbocyclic

25

wherein any one or more of the alkyl carbon atoms is substituted with halo as chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals The term "halo" and "halogen" means halogens such as fluorine,

30

defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chiloromethyl, dichloromethyl, trichloromethyl, dichloropropyl, dichloromethyl, dichloropropyl, dichlorocethyl, adichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

2

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

12

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or more rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and anthracenyl. More preferred aryl is phenyl. Said "aryl" group may have one to three substituents such as lower alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Preferred heterocyclyl are 3-10 membered ring heterocyclyl, particularly 5-8 membered ring heterocyclyl.

೫

WO 00/47568

PCT/US00/02503

9

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidiny], imidazolidinyl, piperidino, piperazinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

- atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiszolidinyl].

  Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5
  - 10 to 6 membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, for example, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl,
    - benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.;
- unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated 5 to 6-
- membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl] and the like. The term also embraces
- 30 radicals where heterocyclic radicals are fused with any radicals. Examples of

PCT/US00/02503

hydroxy, oxo, amino and lower alkylamino Said "heterocyclyl" group may have 1 to 3 substituents such as lower alkyl such fused bicyclic radicals include benzofuran, benzothiophene, and the like

5 one or two heteroatoms selected from sulfur nitrogen and oxygen, selected 3-10 membered fused or unfused radicals. Preferred examples of heteroaryl pyridyl, piperidinyl and pyrazinyl. from thienyl, furanyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, More preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, furyl, and pyrazinyl. dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, Heterocyclic radicals can include fused or unfused radicals, particularly

The term "heteroaryl" means a fully unsaturated heterocyclyl.

molecule of interest can be at the heteroatom or elsewhere within the ring. In either "heterocyclyl" or "heteroaryl," the point of attachment to the

2

heterocyclyl and heteroaryl which contain more than one ring heteroatom and said heterocyclyl and heteroaryl. for which isomers are possible, such isomers are included in the definition of The term "triazolyl" includes all positional isomers. In all other

25 20 the molecule of interest can be at a heteroatom or elsewhere. charged structures). The point of attachment of the quaternary heterocyclyl to the term is intended to encompass both ternary and quaternary positively oxygen, has such a number of bonds that it is positively charged (and therefore or more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or The term "quaternary heterocyclyl" means a heterocyclyl in which one

structures). The point of attachment of the quaternary heteroaryl to the has such a number of bonds that it is positively charged (and therefore the term more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or oxygen, is intended to encompass both temary and quaternary positively charged The term "quaternary heteroary!" means a heteroary! in which one or

8

WO 00/47568 PCT/US00/02503

molecule of interest can be at a heteroatom or elsewhere

points of attachment to molecules of interest The term "diyl" means a diradical moiety wherein said moiety has two

The term "oxo" means a doubly bonded oxygen

having a molecular weight up to about 20,000, more preferably up to about 10,000, and most preferably up to about 5,000. The term "polyalkyl" means a branched or straight hydrocarbon chain

about 20,000, more preferably up to about 10,000, and most preferably up to are replaced by oxygen, wherein the polyether has a molecular weight up to The term "polyether" means a polyalkyl wherein one or more carbons

5

to about 10,000, and most preferably up to about 5,000 the polyalkoxy has a molecular weight up to about 20,000, more preferably up The term "polyalkoxy" means a polymer of alkylene oxides, wherein

20 5 propanediol, glucaric acid and galactaric acid. sedoheptulose, glucosamine, galactosamine, glucoronic acid, galacturonic acid, glucose, mannose, fructose, galactose, ribose, erythrose, glycerinaldehyde, and which belong to the D- or L-series; aminosugars; sugar alcohols; and up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan polysaccharides wherein the polysaccharides can have a molecular weight of gluconic acid, galactonic acid, mannoic acid, glucamine, 3-amino-1,2saccharic acids. Nonlimiting specific examples of such carbohydrates include residue; compounds derived from aldoses and ketoses with 3 to 7 carbon atoms carbohydrates such as, but is not limited to, mono-, di-, tri-, tetra- and The term "carbohydrate residue" encompasses residues derived from

to about 100 amino acid units The term "peptide residue" means polyamino acid residue containing up 25

more preferably from about 100 amino acid units to about 750 amino acid containing from about 100 amino acid units to about 1000 amino acid units The term "polypeptide residue" means a polyamino acid residue

30

PCT/US00/02503

S

untis, and most preferably from about 100 amino acid units to about 500 amino

The term "alkylammoniumalkyl" means an an -NH3 group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

The term "sulfo" means a sulfo group, -SO3H, and its salts.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

2

The term "aralky!" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are lower aralkyl radicals having phenyl attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "arylalkenyl" embraces aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower

aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having The term Theterocyclylalkyl" means an alkyl radical that is substituted

15

with one or more heterocyclyl groups. Preferable heterocyclylalkyl radicals are
"lower heterocyclylalkyl" radicals having one or more heterocyclyl groups
attached to an alkyl radical having one to ten carbon atoms.

The term "heteroary/alkyl" means an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

23

The term "quaternary heterocyclylalkyl" means an alkyl radical that is substituted with one or more quaternary heterocyclyl groups. Preferable quaternary heterocyclylalkyl radicals are "lower quaternary heterocyclylalkyl" radicals having one or more quaternary heterocyclyl groups attached to an alkyl radical having one to ten carbon atoms.

WO 00/47568

PCT/US00/02503

3

The term "quaternary heteroary!alky!" means an alky! radical that is substituted with one or more quaternary heteroary! groups. Preferable quaternary heteroary!alky! radicals are "lower quaternary heteroary!alky!" radicals having one or more quaternary heteroary! groups attached to an alky! radical having one to ten carbon atoms.

S

The term "alkylheteroarylalkyl" means a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

10 The term "alkoxy" means an alkyl radical which is attached to the molecule of interest by oxygen, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and terr-butoxy.

The term "carboxy" means the carboxy group, -CO,H, or its salts.

The term "carboxyalkyl" means an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.

The term "carboxyheterocyclyl" means a heterocyclyl radical that is substituted with one or more carboxy groups.

2

The term "carboxyheteroary!" means a heteroaryl radical that is substituted with one or more carboxy groups.

The term "carboalkoxyalkyl" means an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.

23

The term "carboxyalkylamino" means an amino radical that is mono- or di-substituted When used in combination, for example "alkylaryl" or

30 "arylalkyl," the individual terms listed above have the meaning indicated

above.

not limited to, acetyl and benzoyl. the carboxy group has been removed. Examples of acyl groups include, but are The term "acyl" means an organic acid group in which the hydroxy of

invention that inhibits transport of bile acids The term "active compound" means a compound of the present

of a mammal, such as a human. This includes increasing the fecal excretion of inhibiting absorption of bile acids from the intestine into the circulatory system The term "a bile acid transport inhibitor" means a compound capable of

- 5 prophylaxis and/or treatment by bile acid transport inhibition include, for cholesterol and cholesterol ester, and more specifically, reducing LDL and bile acids, as well as reducing the blood plasma or serum concentrations of VLDL cholesterol. Conditions and/or diseases that benefit from the example, a hyperlipidemic condition such as atherosclerosis.
- 15 The term "THF" means tetrahydrofuran; The abbreviations used in this application have the following meanings:

The term "PTC" means phase transfer catalyst;

The term "Aliquart 336" means methyltricaprylylammonium chloride;

The term "MCPBA" means m-chloroperbenzoic acid;

20 The term "Celite" refers to a brand of diatomaccous earth filtering aid; The term "DMF" means dimethylformamide;

The term "BOC" means t-butoxycarbonyl; The term "DME" means ethylene glycol dimethyl ether,

The term "Me" means methyl;

25 The term "Et" means ethyl;

The term "Bu" means butyl;

The term "EtOAc" means ethyl acetate;

The term "Et,O" means diethyl ether;

The term "LAH" means lithium aluminum hydride;

WO 00/47568

The term "DMSO" means dimethylsulfoxide;

The term "PEG" means polyethylene glycol; The term "KOSiMe," means potassium trimethylsilanolate;

The term "MS" means mass spectrometry;

The term "ES" means electrospray; The term "HRMS" means high resolution mass spectrometry;

The term "GC" means gas chromatography; The term "NMR" means nuclear magnetic resonance spectroscopy;

The term "MPLC" means medium pressure liquid chromatography;

5

chromatography The term "RPHPLC" means reverse phase high pressure liquid The term "HPLC" means high pressure liquid chromatography;

The terms "h" or "hr" means hour(s); and The term "RT" means room temperature;

15 The term "min" means minute(s);

### Alternate Forms of Compounds

such as diastereomers and enantiomers, in both pure form and in admixture. asymmetrical carbon atoms, and therefore include racemates and stereoisomers, The compounds of the present invention can have at least two

25 20 bond. All such isomers are contemplated among the compounds of the present isomers of compounds of the present invention. Isomers may include techniques, either by reacting enantiomeric starting materials, or by separating geometric isomers, for example cis isomers or trans isomers across a double Such stereoisomers can be prepared and separated using conventional

solvates and prodrugs of such compounds. The compounds of the present invention also include tautomers, salts,

PCT/US00/02503

Compound Syntheses

The starting materials for use in the preparation of the compounds of the invention are commercially available or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art. Generally, the compounds of the present invention can be prepared by the procedures described below.

WO 00/47568

PCT/US00/02503

presence of a base, such as triethylamine, in a solvent, such as tetrahydrofuran,

9b. Reaction of benzenesulfonyl chloride 1 with aminoalcohol 2 in the

yields benzenesulfonamide 3 which can be converted to protected

- substituted benzenesulfonamide 5. Protected benzenesulfonamide 4 or Nsuch as sodium hydride, in a solvent, such as dimethylformamide, to yield N. treated with an alkyl halide, such as methyl iodide, in the presence of a base benzenesulfonamide 4. Protected benzenesulfonamide 4 optionally can be
- 5 base (such as n-butyllithium in hexanes) in a solvent (such as tetrahydrofuran) (such as tetrakis(triphenylphosphine)palladium(0)) to yield sulfonamide 6. carbonate), a benzyl halide (such as p-methoxybenzyl chloride), and a catalyst (ii) an electrophile (such as trimethyl borate), and (iii) a base (such as sodium substituted benzenesulfonamide 5 is then successively reacted with (i) a strong Treatment of sulfonamide 6 with a fluoride source, such as
- 20 2 R\* and q are as previously defined above for compounds of Formula I. tetrabutylammonium fluoride, in a solvent, such as tetrahydrofuran, provides oxidized using a method such as Swern Oxidation to yield sulfonamide the deprotected sulfonamide alcohol 7. Sulfonamide alcohol 7 is successively aldehyde 8 is converted to racemic benzothiazepines 9a and 9b. R!, R?, R!, R!, R! aldehyde 8. Upon treatment with a base such as potassium tert-butoxide,

WO 00/47568

PCT/US00/02503

#### SCHEME 2

## Alternative Synthesis of sulfonamide alcohol

SO<sub>2</sub>CI HO NH<sub>2</sub> Ei<sub>3</sub>N SO<sub>2</sub>NH 
$$R^{1}$$
R<sup>2</sup> OH

10 11 12

Where L = F, Cl, Br, NO<sub>2</sub>, TsO, TfO  $(R^{5})_{a}$ M  $R^{1}$ R<sup>2</sup> OH

5 I. Substituent M is a metal, preferably an alkali metal, or a hydrogen. 1. R', R2, R\* and q are as previously defined above for compounds of Formula benzenesulfonamide 3 which can be further reacted in accordance with Scheme base, such as triethylamine, in a solvent, such as tetrahydrofuran, yields Reaction of sulfonamide 12 with a suitable nucleophile in the presence of a as fluoro, chloro, bromo, nitro, tosyloxy or trifluoromethylsulfonyloxy. Substituent L of benzenesulfonyl chloride 10 is a suitable leaving group such triethylamine, in a solvent, such as tetrahydrofuran, yields sulfonamide 12. chloride 10 with aminoalcohol 11 in the presence of a base, such as of sulfonamide alcohol 3 used in Scheme 1. Reaction of benzenesulfonyl Scheme 2 illustrates an alternative synthetic scheme for the preparation

Scheme 3 illustrates the preparation of benzothiazepines having 4position substituents other than hydroxy.

Swern conditions can be used. Benzothiazepine-4-one 13 is then reacted with benzothiazepine-4-one 13. Conventional oxidizing agents, such as PCC, or lithium aluminum hydride, in a suitable solvent, such as tetrahydrofuran, to benzothiazepine 14 can be reacted with a suitable reducing agent, such as Lawesson's Reagent to produce 4-thioxo-benzothiazepine 14. 4-Thioxo-In the preparation of 4-thioxo-, thio-, sulfinyl- or sulfonylbenzothiazepines, benzothiazepine 9a or 9b is first oxidized to

reacted with a suitable alkylating agent, such as an alkyl halide, in the presence yield 4-mercapto-benzothiazepine 15. 4-Mercapto-benzothiazepine 15 can be benzothiazepine 16 can be reacted with a suitable oxidizing agent, such as tdimethylformamide, to yield 4-alkylthio-benzothiazepine 16. 4-Alkylthiobutyl hydroperoxide or m-chloroperbenzoic acid, to yield, successively, 4alkylsulfinyl-benzothiepine 17 and 4-alkylsulfonyl-benzothiazepine 18. of a base, such as sodium hydride, in a suitable solvent, such as 12 2

Alternatively, 4-amino- or imino-benzothiazepines can be prepared by suitable solvent, such as tetrahydrofuran, to produce 4-imino-benzothiazepine reacting benzothiazepine-4-one 13 with ammonia or a primary amine in a

sodium triacetoxyborohydride, in a suitable solvent, such as tetrahydrofuran, to 19. 4-Imino-benzothiazepine 19 can be reacted with a suitable reducing agent, tetrahydrofuran, to yield 4-amino-benzothiazepine 20. Benzothiazepine-4-one 13 also can undergo reductive alkylation by reaction with ammonia, a primary amine or a secondary amine in the presence of an reducing agent, such as such as lithium aluminum hydride, in a suitable solvent, such as 2

Scheme 3 also illustrates the preparation of 4-alkyl-benzothiazepine 23 and 4-alkoxycarbonyl-benzothiazepine 25. The 4-position hydroxy of produce 4-amino-benzothiazepine 21.

22

mesyloxy to form protected benzothiazepine 22. Protected benzothiazepine 22 benzothiazepine 9a or 9b is first converted to a suitable leaving group such as 2

reaction with a suitable alcohol in the presence of a base, such as potassium benzothiazepine 24 is converted to 4-alkoxycarbonyl-benzothiazepine 25 by dimethylformamide, to yield 4-cyano-benzothiazepine 24. 4-Cyanocyanidating agent, such as an potassium cyanide, in a suitable solvent, such as is then reacted with a suitable nucleophile, such as butyl lithium, in a suitable Alternatively, protected benzothiazepine 22 can be reacted with a suitable solvent, such as tetrahydrofuran, to yield 4-alkyl-benzothiazepine 23.

٧,

Scheme 4 illustrates the preparation of benzothiazepine-4-ene 36 and benzothiazepine-4-one 33. Reaction of phenol 26 with a thiocarbamyl chloride, such as dimethylthiocarbamyl chloride, in a solvent, such as methanol:tetrahydrofuran yields O-thiocarbamate 27. Heating of O-thiocarbamate 27 in a solvent, such as tetradecane, yields 5-thiocarbamate 28. Hydrolysis of 5-thiocarbamate 28 in the presence of a base, such as sodium

- bitiocarbamate 27 in a solvent, such as tetradecane, yields 5-thiocarbamate 28.

  Hydrolysis of 5-thiocarbamate 28 in the presence of a base, such as sodium hydroxide, in a solvent, such as methanol:tetrahydrofuran, yields thiophenol 29. Thiophenol 29 can be treated with a sulfonylating agent, such as sulfonyl chloride, in the presence of a oxidant such as potassium nitrate, in a solvent, such as tetrahydrofuran, to yield sulfonyl chloride 30. Sulfonyl chloride 30 is then reacted with an aminoalcohol in a solvent, such as tetrahydrofuran, to yield benzenesulfonamide 31. Benzenesulfonamide 31 optionally can be hydroxyl protected with a silylating group agent, such as terr-
- butyldimethylsityl chloride, in the presence of a base, such as imidazole, in a solvent, such as tetrahydrofuran, to yield protected benzenesulfonamide 32.

  Protected benzenesulfonamide 32 can be treated with an alkyl halide, such as methyl iodide, in the presence of a base such as sodium hydride, in a solvent, such as dimethylformamide, to yield N-substituted benzenesulfonamide 33.

  Deprotection of the protected N-substituted benzene sulfonamide 33 with a fluoride source, such as tetrabutylammonium fluoride, in a solvent, such as tetrahydrofuran, yields N-substituted benzenesulfonamide 34 is then oxidized with a suitable oxidizing agent or under Swern conditions to form aldehyde 35. Upon treatment with zinc and titanium trichloride aldehyde 35 is converted to a mixture of benzothiazepine-4-ene 36 and benzothiazepine-4-one

The recovery, isolation and purification of the intermediates and the reaction products of this invention, and in particular the intermediates and the reaction products illustrated in Schemes 1, 2, 3 and 4, can be accomplished by conventional methods well known to those skilled in the art, such as

8

WO 00/47568

PCT/US00/02503

76

precipitation, filtration, extraction, or chromatography. Except where otherwise indicated, conditions, solvents, and reagents are either conventional, not narrowly critical, or both.

## Additional Embodiments and Examples

Another class of compounds of specific interest comprises those compounds of Formula I wherein R¹ and R² are selected from among substituted and unsubstituted C₁₁₀ alkyl wherein substituted C₁₁₀ alkyl comprises one or more radicals independently selected from among, for example, alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocyclyl joined to the C₁₊₀ alkyl through an ether linkage. These R¹ and R² substituents include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, CH₂C(=O)C₂H₃, -CH₂OC₂H₃, and -CH₂ O-(4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R¹ and R² are identical, for example n-butyln-butyl, so that the compound is achiral at the 3-position carbon. Eliminating optical isomerism at the 3-position carbon simplifies the selection, synthesis,

In the compounds of the present invention having a chiral 3-position carbon as well as those having an achiral 3-position carbon as well as those having an achiral 3-position carbon, substituents R\* on the benzo ring can include, for example, hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-carbonylalkylamino, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, amino, N-alkylamino, N,-dialkylamino, (N)-

separation, and quality control of the compound used as an ileal bile acid

transport inhibitor.

2

25 alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamoyl, trialkylammonium (especially with a halide counterion), (N)-amido, (N)-alkylamido, N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-baloalkylsulfonamido, carboxyalkylamino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamino

a halo or a quaternary ammonium salt, and (N)-nitrogen containing

heterocyclyl wherein the nitrogen of said heterocyclyl is optionally

isopropyl, t-butyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, Among the preferred species which may constitute R\* are methyl, ethyl,

ᅜ 5 methylpiperazinyl, (N)-bromomethylamido, (N)-N-hexylamino, thiophene, methylpyridinium A-, (N)-N-methylmorpholinium A-, and N-N'azetidinyl, (N)-N-methylazetidinium A-, (N)-pyrrolidinyl, pyrrolyl, (N)-Nhydroxylamino, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, NHC(=0)C3H11, -NHC(=0)C6H12, carboxyethylamino, (N)-morpholinyl, (N)benzyloxycarbamoyl, trimethylammonium A; -NHC(=0)CH3, -

20 disubstituted at the 7- and -8 positions. Also included are the 6,7,8-trialkoxy -(OCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>], where A is a pharmaceutically acceptable anion. The benzo ring can be mono-substituted at the 6, 7 or 8 position, or

t-butyloxycarbamoyl, (N)-methylsulfonamido, (N)N-methylpyrrolidinium, and N+(CH<sub>3</sub>)<sub>2</sub> CO<sub>2</sub> H I; -NCH<sub>3</sub> CH<sub>2</sub> CO<sub>2</sub>H, -(N)-N'-dimethylpiperazinium I; (N)-

residue (e.g., a 5 or 6 carbon monosaccharide residue), peptide residue, and e.g., -(OCH2 CH2), -N+R 13R14R15A; where x is 2 to 10. quaternary ammonium salts linked to the ring via poly(oxyalkylene) linkages the benzo ring including, for example, guanidinyl, cycloalkyl, carbohydrate substituents can be advantageously present on the 6, 7, 8, and/or 9- positions of compounds, for example the 6,7,8-trimethoxy compounds. A variety of other

23

unsubstituted aryl, thiopene, pyridine, pyrrole, thiazole, imidazole, pyrazole independently selected from among hydrogen and ring-carbon substituted or In further compounds of the present invention, R5 and R6 are

30

PCT/US00/02503

WO 00/47568

alkylamino, N,N-dialkylamino, quaternary ammonium salts, a C, to C. pyrimidine, morpholine, N-alkylpyridinium, N-alkylpiperazinium, Namong, for example, halo, hydroxyl, trihaloalkyl, alkoxy, amino, Nalkylmorpholinium, or furan in which the substituent(s) are selected from

5 alkoxycarbonyl, aryloxycarbonyl, alkylcarbonyloxy and arylcarbonyloxy alkylene bridge having a quaternary ammonium salt substituted thereon, phenyl, phenylene, or benzene triyl, i.e., may be unsubstituted, monocomprises halo or a quaternary ammonium salt, thiophene, pyridine, pyrrole, (O,O)-dioxyalkylene, -[O(CH<sub>2</sub>)<sub>d</sub>]<sub>e</sub>X where e is 2 to 12, d is 2 or 3 and x thiazole, imidazole, pyrazole, or furan. The aryl group of R5 or R6 is preferably

substituted, or di-substituted. Among the species that may constitute the substituents on the aryl ring

ᅜ methoxycarbonyl, ethoxycarbonyl, formyl, acetyl, propanoyl, (N)of R5 or R6 are fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, trimethylammonium (preferably with an iodide or chloride counterion),

Other substituents that can be present on a phenylene, benzene triyl or other each substituted at the p-position, the m-position, or both of the aryl ring. tri(oxyethylene)iodide, and tetra(oxyethylene)trimethyl-ammonium iodide, hexyldimethylammonium, hexylenetrimethylammonium,

20 methoxyphenyl, p-N,N-dimethylaminophenyl, m-N, N-dimethylaminophenyl, fluorophenyl, p-hydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, mthose in which R' or R' is selected from phenyl, p-fluorophenyl, mdioxyethylene (6-membered ring). One group of compounds of interest are aromatic ring includes 3, 4-dioxymethylene (5-membered ring) and 3, 4-

ಕ 25 methoxyphenyl, 4-pyridinyl, 2-pyridinyl, 3-pyridinyl, N-methyl-4-pyridinium (N,N-dimethylpiperazinium)-(N')-CH<sub>2</sub>-OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>-O-phenyl, 3-fluoro-4fluorophenyl, thienyl-2-yl, 5-cholorothienyl-2-yl, 3, 4-difluorophenyl, I-p-(N,N-dimethylpiperazinium)-(N')-CH2-(OCH2CH2)2-O-phenyl, 3-methoxy-4-I' p-(CH<sub>3</sub>)<sub>3</sub>-N<sup>\*</sup>-phenyl, I' m-(CH<sub>3</sub>)<sub>3</sub>-N<sup>\*</sup>-phenyl, I' m-(CH<sub>3</sub>)<sub>3</sub>-N<sup>\*</sup>-CH<sub>2</sub>CH<sub>2</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>-O-phenyl, I' p-(CH<sub>3</sub>)<sub>3</sub>-N'-CH<sub>2</sub>CH<sub>2</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>-O-phenyl, I' m-

I N-methyl-3-pyridinium, 3, 4-dioxymethylenephenyl, 3, 4dioxyethylenephenyl, and p-methoxycarbonylphenyl.

compounds having each of the above preferred R3 substituents in combination with the R\* substituents shown in Tables 1, 2 and 3 below. It is particularly Preferred compounds include 3-ethyl-3-butyl and 3-butyl-3-butyl preferred that one, but not both, of R5 and R6 is hydrogen.

be hydrogen, and that R3 and R3 be oriented in the same direction relative to the It is especially preferred that R\* and R\* be hydrogen, that R3 and R3 not plane of the molecule, i.e., both in a. or both in \theta-configuration. It is further preferred that, where R2 is bulyl and R1 is ethyl, then R1 has the same

orientation relative to the plane of the molecule as R3 and R3.

2

second part of Table 1 identifies the R' radical or radicals for those compounds. Table 1 identifies the R1, R2, R3, R4 and R2 radicals for each compound and the benzothiazepines wherein the R', R', R' and R' radicals are as set forth in Table 1 below; the Re radical is hydrogen; the Re radical is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, nfrom the group of R' radicals disclosed in Table 1 below. The first part of hexyl and benzyl; and the R\* radical or radicals are independently selected A class of compounds of particular interest comprises those 1,2-

2

equ')

equ')

equ')

equ')

equ')

equ')

equ')

equ')

equ')

equ') 4-(decyloxy)phenyl phenyl phenyl phenyl u-pntλ|
u-pntλ|
u-pntλ|
u-pntλ|
u-pntλ|
ettλ|
u-pntλ|
u-pntλ|
u-pntλ| HO HO HO HO HO HO HO HO 601 801 201 901 \$01 \$01 201 101 HHHHHHH prenyl prenyl ушроппд Митрет Вγ ЪЯ КЗ Въ В

> (K<sub>x</sub>)<sup>d</sup> Ig mm

> > I AJBAT

WO 00/47568

PCT/US00/02503

8

PCT/US00/02503

s

. يخي عي

11	110	ethyl	n-butyl	OH	Н	phenyi
13	111	n-butyl				pitchyl
H <sub>2</sub> N	112	ethyl	n-butyl			0, 0
13						S-N
14	113					
15						
17   n-butyl   ethyl   OH   H   phenyl     18   ethyl   n-butyl   OH   H   phenyl     19   ethyl   n-butyl   OH   H   phenyl     20   n-butyl   ethyl   OH   H   phenyl     21   ethyl   n-butyl   OH   H   phenyl     22   n-butyl   ethyl   OH   H   phenyl     23   n-butyl   ethyl   OH   H   phenyl     24   n-butyl   ethyl   OH   H   phenyl     25   n-butyl   ethyl   OH   H   phenyl     26   n-butyl   ethyl   OH   H   phenyl     27   n-butyl   ethyl   OH   H   phenyl     28   n-butyl   ethyl   OH   H   phenyl     30   n-butyl   ethyl   OH   H   phenyl						
17	116					
18         cthyl         n-butyl         OH         H         phenyl           19         ethyl         n-butyl         OH         H         phenyl           20         n-butyl         ethyl         OH         H         phenyl           21         ethyl         n-butyl         OH         H         phenyl           22         n-butyl         ethyl         OH         H         phenyl	117					
19	118					
20         n-butyl         cthyl         OH         H         phenyl           21         cthyl         n-butyl         OH         H         phenyl           22         n-butyl         cthyl         OH         H         phenyl	119					
21         ethyl         n-butyl         OH         H         phenyl           22         n-butyl         ethyl         OH         H         phenyl	120				Н	
22 n-butyl ethyl OH H phenyl	121	ethyl	n-butyl	OH ·		
	122	n-butyl				
23 ethyl n-butyl OH H phenyl	123	ethyl	n-butyl	OH	н	

	phenyl	H	OH	ethyl	n-butyl	124
	phenyl	н	ОН	n-butyl	ethyl	125
	4-fluorophenyl	н	OH	ethyl	n-butyl	126
	4-fluorophenyl	н	OH	ethyl	n-butyl	127
	4-fluorophenyl	н	OH	n-butyl	ethyl	128
	4-fluorophenyl	н	OH	n-butyl	ethyl	129
	4-fluorophenyl	Н	OH	n-butyl	ethyl	131
	phenyl	Н	ОН	n-butyl	ethyl	132
	phenyi	Н	OH	n-butyl	ethyl	133
	phenyl	н	OH	n-butyl	ethyl	134
	phenyl	H	ОН	n-butyl	ethyl	135
——	phenyl	н	ОН	n-butyl	ethyl	136
	phenyl	н	· OH	ethyl	n-butyl	137
	phenyl	н	OH	ethyl	n-butyl	138
	Phenyl	н	OH	ethyl	n-butyl	139
	H	OH	Н	n-butyl	ethyl	142
	3-methoxyphenyl	н	ОН	n-butyl	ethy!	143
	4-fluorophenyl	H	OH	n-butyl	ethyl	144
	3-methoxyphenyl	H	OH	n-butyl	ethyl	262
	Н	OH	Н	n-butyl	ethyl	263
نواهذ	3-trifluoromethylphenyl	н	OH	n-butyl	ethyl	264
	Н	OH	Н	n-butyl	ethyl	265
	3-hydroxyphenyl	Н	OH	n-butyl	ethyi	266
	3-bydroxyphenyl	н	OH	n-butyl	ethyl	267
——	4-fluoropheny)	H	ОН	n-butyl	ethyl	268
	H H	OH	Н	n-butyl	ethyl	269
	4-fluorophenyl	Н	ОН	n-butyl	ethyl	270
	3-methoxyphenyl	н	ОН	n-butyl	ethyl	271
	H	OH	н .	n-butyl	ethyl	272
	н н	OH	Н	n-butyl	ethyl	273
	4-fluorophenyl	H	ОН	n-butyl	ethyl	274
	+ nadiopachyi	OH	н	n-butyl	ethyl	275
	3-methoxyphenyl	н	OH ·	n-butyl	ethyl	276

1 N(CH <sup>3</sup> ) <sup>3</sup>	н	но	, jáng-u	εφλη	967
1,100	н	но	ıkınq-u	בוףאן	567
руспуд	н	но	Ivind-ii	I/Jud-a	767
bpenA <sub>f</sub>	Н	но	n-pntyl	IVind-a	293
4-fluorophenyl	н	но	ηέλησ-α	η/ληνο-α	262
ppenAj	н	но	Ivind-a	n-butyl	167
Бреиду	Н	HO .	[ʎɪnq-a	υ-ραίλι	067
русид	н	но	lytud-a	υ-ραιλί	687
ррепу	н	но	Inethyl	τυετρλί	288
русий	Н.	но	ctbyl	сұуλ]	L87
рбенуј	H	но	сфу	εφλι	286
4-thorophenyl	Н	но	p-prtyl	cmyl	787
H	НО	H	[Anq-a	сфуј	283
4-fhorophenyl	н	НО	p-pris)	сџуј	787
-fluorophenyl	H	но	p-prtyl	emyl	187
2-Плоторhелу!	Н	но	j/snq-a	сгръј	087
3-thorophenyl	HO_	н	[Anq-a	capyl	6LZ
у-гілогорьспуі	но	н	[{\psi}nq-a	сцуј	278
3-fluorophenyl	н	но	n-butyl	crpλg	LLZ

PCT/US00/02503

1004	ethyl	n-butyl	ОН	Н	· \
					CF <sub>3</sub> COO- + (CH <sub>3</sub> CH <sub>2</sub> ) <sub>3</sub> N
1005	n-butyl	n-butyl	ОН	н	CF <sub>3</sub> COO- (CH <sub>3</sub> CH <sub>2</sub> ) <sub>3</sub> N
1006	n-butyl	n-butyl	ОН	н	$\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$

1007	n-butyl	n-butyi	OH	н	<u> </u>
					+ I- N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1008	n-butyl	n-butyl	OH	н	
1009	n-butyl	n-butyl	· OH	н	1. + N
1010	n-butyl	n-butyl	ОН	Н	3-fluoro-4-methoxyphenyl
1011	n-butyl	n-butyl	ОН	н	3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt
1012	n-butyl	n-butyl	OH	H	4-hydroxyphenyl

PCT/US00/02503

_	·					
	O CO2H					
$\downarrow$		н	но	I-pn(),	n-butyl	9101
60	Br. Ar.	н	но	u-pniλj	u-pnţλ <u>ı</u>	\$101
_	<ul><li>ф-шеірохуррену</li></ul>	н	но	n-park)	υ-ρπιλη	1014
	ε(cH <sub>3</sub> ) <sub>3</sub> + Γ-					
Ц_	. э. 🗸 ( ,	Н	НО	a-praij	υ-ρπέλ <u>ι</u>	1013

1019	n-butyl	n-butyl	ОН	н	CF <sub>3</sub> CO <sub>2</sub>
1020	n-butyl	n-butyl	OH .	Н	CI- N(CH <sub>2</sub> CH <sub>3</sub> )
1021	n-butyl	n-butyl	ОН	Н .	I- OH

1022	n-butyl	n-butyl	ОН	Н	I- О — 3 — ОН
1023	n-butyl	n-butyl	OH	Н .	I- N-

88
55
ş
8
₹

	HO + + 1	н	но	u-pniyl	j.Kinq-a	1028
26	+ N -1	н	но	J∕sinq-a	¡Kınq-u	<i>L</i> 201
	+ 0 1	н	но	į kiną-a	lV1ud-a	9701

	N(CHFCHP)	н	но	į Kınq-u	[£inq-u	\$201
8		== .				
				- -		
	N—		• •			
	+ 1					
	-1	н	но	lÇinq-u	и-рлиλן	<b>†</b> Z01

1029	n-butyl	n-butyl	ОН	H	I. + + + + + + + + + + + + + + + + + + +
1030	n-butyl	n-butyl	ОН	Н	1- N + + N S
1031	n-butyl	n-butyi	ОН	н	CF <sub>3</sub> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub> O O N(CH <sub>2</sub> CH <sub>3</sub> ) +

1032	n-butyl	n-butyl	OH .	н	CF <sub>3</sub> CO <sub>2</sub> + N(CH <sub>2</sub> CH <sub>3</sub> )
1033	n-butyl	n-butyl	OH .	H	F N Br-

созснзснз

95

-1	н	но	JAinq-u	j.Kinq-a	<b>▶</b> €01

lytud-a

o-pntyl

n-butyl

9801

n-pressy

HO

WO 00/47568

PCT/US00/02503

1038	n-butyl	n-butyl .	OH	н	I- + N(CH <sub>3</sub> ) <sub>3</sub>
1039	n-butyl n-butyl	n-butyl n-butyl	OH OH	н н	F CF <sub>3</sub> CO <sub>2</sub>
1041	n-butyl	n-butyl	ОН	н	0 0 N(CH <sub>2</sub> CH <sub>3</sub> ) +
			·		

1042	n-butyl	n-butyl	ОН	Н	I- N(C <sub>6</sub> H <sub>5</sub> )
1043	n-butyl	n-butyl	ОН	н	
1044	n-butyl	n-butyl	ОН	Н	F CF <sub>3</sub> CO <sub>2</sub> + N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1045	n-butyl	n-butyl	ОН	Н	CF <sub>3</sub> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>8</sub> + N(CH <sub>2</sub> CH <sub>3</sub> )
1046	n-butyl	n-butyl	OH	H	3-aminophenyl

	+ N -1 -1	н	. но	Įćīną-u	Į≮inq-u	<b>Z</b> \$01
001	CE3CO2	н		j&inq-a	-par2	1501
	+ N - 1 O - 1	н.	но	a-parkl	Į∕sinq~u	0501

						•
44	E Br	н	но	Į£įnq-u	I¢inq-u	6901
	1- (CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup>	н	но	ı Çinq-u	r-pniyl	8 <b>+</b> 01
	N(CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup>					
	1,	н	но	fytud-a	u-pntλj	<b>∠</b> ₩01

1053	n-butyl	n-buty!	ОН	н	F CF <sub>3</sub> CO <sub>2</sub>
1054	n-butyl	n-butyl	ОН	н	1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1

1055	n-butyl	n-butyl	ОН	н	1- N+ N
1056	n-butyi	n-butyl	ОН	н	1- 1- 1- 1- 1- 1-
1057	n-butyl	n-butyl	ОН	Н	1- N + N

401	-1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -	н	но	гориду	јАлпq−и	£901
L		Н	HO	lyind-a	n-butyl	1007
L		Н	но	n-buryl	r-pntA	75

_						
			·		·	
- (		н	но	n-butyl	υ-ρπέλι	1901
ŀ	3-fluoro-4-methoxyphenyl	н	но	n-butyl	сфуј	1000
10.9	De la Br-		но	Jámq-a	l⁄zinq-u	6501
	1 <u> </u>	н	но	t-prtyl	n-butyl	8501

1064	n-butyl	n-butyi	ОН	н	
1065	n-butyl	n-butyl	OH	Н	1- + N((CH <sub>2</sub> CH <sub>2</sub> O) <sub>2</sub> CH <sub>3</sub> )

1066	n-butyl	n-butyl	ОН	Н	r
1067	n-butyl	n-butyl	OH	н	thiophen-3-yl
1068	n-butyl	n-butyl	OH	Н	I- +
1069	n-butyl	n-butyl	ОН	Н	phenyl phenyl
1070	n-butyl	n-butyl	ОН	Н	F CF <sub>3</sub> CO <sub>2</sub>

4-bydroxypbenyl	H	но	n-park	ειγλί	8/01
3-իչժա×փաշանիլինում	H	но	fytud-a	[\timed-m	LLOI
I- + (CH <sub>3</sub> ) <sub>3</sub>	н	но	Ikinq-a	lçind-a	9401
←Ωποτορήσην]	<u>н</u>	HO	IVING-EI	n-prityl	5/01
3-fluoro-4-methoxyphenyl	н	НО	n-butyl	ethyl	\$201 \$201
N + N O					

	1 + + + + + + + + + + + + + + + + + + +	н	но	п-ракλу	n-pniyl	<b>7</b> /01
4			_ AO	panga	para a	
ļ	, N——		•			
	5,		1			
	N C T					
1	-1					
- 1		12	מנו	ιλιπα-α	υ-οπέλι	1/01

1079 ethyl n-butyl OH H	
-------------------------	--

1080	n-butyl	n-butyl	ОН	н .	
1081	n-butyl	n-butyl	OH	Н	1
1082	n-butyl	n-butyl	OH	Н	2-pyridyl
1083	n-butyl	n-butyl .	ОН	H	I- O 3 N +

411	\$ -1	н	но ·	į/sinq-u	į Kanq-a	1601
		н	но	[έιρη-π	lçind-ü	0601

<del>(-</del> шедюхурусну)	Н	но	l/tind-ti	ctbyl	6801
3,4-methylenedioxyphenyl	Н	но	p/snq-u	crpyl	8801
N -1					
	н	но	u-pntyl	l/Jud-n	£801
ly-E-mádoith	H	HO HO	n-pntyl	n-butyl	5801 9801
+ 0 - 1					
	н	но	ը/փոզ-ս	n-butyl	1084

1092	n-butyl	n-butyl	OH	Н	1- 0 1- 3 1+
1093	n-butyl	n-butyl	ОН	н	
. 1094	n-butyl	n-butyl	ОН	Н	1- 1- 1- 1- 1- 1-

1095	n-butyl	n-butyl	ОН	н	
1096	n-butyl	n-butyl	OH	н	1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1
1097	n-butyl	n-butyi	ОН	н	O Br

1/dpix/d-f	но	lyind-a lyind-a	pAmq-u pAmq-u	8011 8011
	НО	lyind-a	Ivind-n	8011
ng H	но	n-butyl	լ (Հրոգ–ա	<u> </u>
Н 3-рудгохурьспу1	HO	υ-ρηιλ]	1/ytud-m	9011
H 3-hydroxyhdenyl	но	IA)nq-u	ικινό-α	5011
E O H	но	kand-n	/sinq-u	<b>≯</b> 011

	1- (CCH <sub>3</sub> )	н	но	J <b>∆</b> inq <b>−a</b>	Kinq-u	£011
2	3-сягрох\писцу\фусц\]	Н	НО	I\(\text{rud-a}\)	I/Unq-u	1102
	t cc <sub>1</sub> co <sub>2</sub> .	н	но	<b>-</b> -թուհլ	a-prayl	1011
ı	ф-шефохурьнуй	Н	но	n-butyl	a-butyl	1100
ı	4-тегрохурьсту	н	HO	p-pntyl	сфλј	6601
	O (CH <sup>2</sup> CH <sup>3</sup> ) <sup>3</sup>					
	. 4	н	но	n-butyl	n-butyl	8601

			077	77	
1110	n-butyl	n-butyl	ОН	Н	1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1
1111	n-butyl	n-butyl .	ОН	н .	F CF <sub>3</sub> CO <sub>2</sub> CO <sub>2</sub> H
1112	n-butyl	n-butyl	OH	H	4-pyridyl
1113	a-butyl	n-butyl	ОН		F ON
1114	n-butyl	n-butyl	OH	Н	3-methoxyphenyl
1115	n-butyl	n-butyl	ОН	H	4-fluorophenyl
1116	ethyl	n-butyl	OH	Н	3-tolyl

1117	ethyl	n-butyl	ОН	н	I- + N(CH <sub>3</sub> )
1118	ethyl	n-butyl	OH	н	3-fluoro-4-hydroxyphenyl
1119	n-butyi	n-butyl	OH	н .	1- N+ N+
1120	n-butyl	n-butyl	ОН	Н	1- 0- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1- 1-

ф-сувпотстурьнуй по	Н	НО	I-butyl	I\(\frac{1}{2}\)	EELL
-1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -					
←шефохуррену!	H	но	lytud-a	I-butyl	1135
	Н	HO.	n-priAt	сфуј	1511
3-chloro-4-fluorophenyl	н	НО	n-butyl	l\zud-a	1130
4-ilvorophenyl	н	HO	ίχιτα-α	υ-ρπέλι	6711
3-fluoro 4-bydroxyphenyl	н	НО	lytud-a	n-buryi	1178
	·				
g I	Iн	но	n-buryl	ikina-a	1127

1126 ctdy		·					
1125		- [					
1157	L			HO_			1176
1153 a-pni) a-pni) OH H Dpca)		3-chloro-4-methoxyphenyl					
1152 B-Puryl OH H (CH2CH3)		3-тегьохурьсту!					
	a	Бреил	н	HO	lytud-a	n-butyl	1123
		+ 1 1	н		18m9-a	j£jng-a	
			н	но	ο-ραιλι	u-parkj	1211

1134	ethyl	n-butyl	ОН	н	
1135	n-butyl	n-butyl	OH	H H	3,4-dimethoxyphenyl
1136	n-butyl	n-butyl	OH		
1137	n-butyl	n-butyl	OH	Н	4-fluorophenyl
1138	n-butyl	n-butyl	ОН	Н	1- N+ +
1139	n-butyl	n-butyl	ОН	H	3,4-difluorophenyl
1140	n-butyl	n-butyl	OH	H	3-methoxyphenyl

1141	n-butyl	n-butyl	OH	Н	4-fluorophenyl
1142	n-butyl	n-butyl	OH	Н	F N(CH <sub>2</sub> CH <sub>3</sub> )
1143	n-butyl	n-butyl	Н	ОН	H
1144	n-butyl	n-butyl	OH	H	5-piperonyl
1145	n-butyl	n-butyl	ОН	Н	4-methoxyphenyl
1146	n-butyl	n-butyl	OH	Н	I (CH <sub>2</sub> ) <sub>1Q</sub> N(CH <sub>3</sub> ) <sub>3</sub> +
1147	n-butyi	n-butyl	OH	H	
1148	n-butyl	n-butyl	OH	H	4-fluorophenyl
1149	n-butyl	n-butyl	ОН	Н	4-fluorophenyl
1150	n-butyl	n-butyl	OH	Н	3-methoxyphenyl
1151	n-butyl	ethyl	ОН	Н	3-fluoro-4-methoxyphenyl
1152	n-butyl	n-butyl	OH	Н	phenyl
1153	n-butyl	n-butyl	OH	н	4-fluorophenyl
1154	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1155	n-butyl	n-butyl	OH	н	4-fluorophenyl
1156	n-butyl	n-butyl	OH	н	4-fluorophenyl
1157	n-butyl	n-butyl	OH	Н	4-fluorophenyl
1158	n-butyl	n-butyl	ОН	Н	4-pyridinyl, hydrochloride salt
1159	n-butyl	ethyl	OH	н	phenyl
1160	n-butyl	n-butyl	OH	H	. 4-fluorophenyl

4-тейьохурденуі	H	НО	lytud-n	lytud-n	5611
HO HO					
/ / / / / / / / / / / / / / / / / / /	H	НО	lyind-a	l/mq-tr	1194
4-(2-(2-methylpropyl))phenyl	н	НО	Iviud-a	lyind-a	1193
3-(dimethylamino)phenyl	н	но	lytud-a	lyind-a	1192
4-(dimethylamino)phenyl	H	HO	lynd-a	jking-u	1611
Z-promobueny.	Н	НО	lytud-n	n-butyl	0611
lynadqorouflib-9,5	H	но	n-butyl	lγtud-α	6811

4-methoxyphenyl	Н	НО	I-butyl	Ivind-n	1188
-fluorophenyl	н	НО	n-butyl	n-park	4811
репу	н	НО	u-pntyl	п-ракуі	9811
4-плогорьспу1	н	НО	IVino-n	n-butyl	2811
4-гупогорьелу!	н	НО	I/mq-u	n-park]	1184
3-тефохурнену!	H	но	n-butyl	n-butyl	1183
4-(diracthylamino)phenyl	н	НО	B-butyl	1/3nq-ti	1182
4-fluorophenyl	H	но	n-parki	D-butyl	
руспуј	Н	но	I/Jnq-u	Içind-n	1811
bpcnAj	H	но	I-butyl	n-prityl	0811
3-(milluoromethylsulfonyloxy)phenyl	H	HO	n-butyl	Içind-n	6411
3-methoxyphenyl	H	HO	I/Jung-u	Içind-n	8411
4-fluorophenyl	- H	но	D-prity(	I-butyl	<u>LL11</u>
3-methoxyphenyl	н н	HO	Içtud-a	сцуј	9/11
3-тейохуриспу!	H	HO	D-butyl	cthyl	\$411
4-гиолористу!	H	HO	ם-פונאן		1/1
-pyridinyl	H	HO	lytud-a	[Anq-u	1173
← (αι[[notoutctp\]ran[[ou\]ox\)bpcu\]	H	HO	lytud-n	a-butyi n-butyi	7/11
3-methoxyphenyl	H	HO	lynd-n		1/11
bpcuAj	H H	HO		lynd-n	0/11
4-bydroxyphenyl	H	HO.	a-butyl a-butyl	lçınd-a lçınd-a	6911 8911
CI	н	но	Į∕smq-u	IV:nq-a	<i>L</i> 911
3-руфохурьсту!	H	но	α-ρητλι	n-prityl	9911
3-fluoro-4-methoxyphenyl	H	но	u-pnth	l/tind-a	9911
lynibiryq-▶	- н	но	I-bush	I/QINQ-U	
3-(dimethylamino)phenyl	H	HO	u-pntλj	n-butyl	1100
bycuAl	H	но	n-buryl	n-prityl	1103
3,5-dichloro-4-methoxyphenyl	H	HO	I/Sind-a		1102
1 ( All-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-		NO I	lund-a	l\z\nd-a	1911

	5	
è	3	
Š		
ξ	Š	

1196	n-butyl	n-butyl	OH	н	I + + N(CH3)
1197	n-butyl	ethyl	R3 + R4 =	R3 + R4 =	phenyl
1198	n-butyl	n-butyl	OH	Н	4-(pyridinyl-N-oxide)

125

1199	n-butyl	n-butyl	<b>ОН</b>	н	HO, In the second secon
1200	n-butyl	n-butyl	н	ОН	H
1201	n-butyl	n-butyl	OH	н	Н

ф-шегрохурьстуг .	Н	но	n-prityl	1-fand-a	1718
4-carboxyphenyl	н н	но	n-butyl	I-butyl	
γίσουσμος	<u>н</u>	НО	n-park	cqr\l	2171 9171
4-methoxyphenyl	Н	HO	1/Jmq-ti	u-prt/s	5121
phenyl	Н	НО	cqvAj	ιλιπα-α	1214
н	НО	н	сфуј	J/Jmq-tz	1213
4-methoxyphenyl	Н	НО	J/Jnq-u	u-prikj	7171
E O O O O O O O O O O O O O O O O O O O	н	но	J43nq− <b>u</b>	€ द्युके	1121

2-(directlylamino)phenyl	н	но	n-press	μέρης-u	1210
русод	H	acctoxy	n-butyl	Içind-n	6071
ф-шефохуруену!	н	но	D-pntyl	ı/sınq-tı	8071
lymsdqoroldsib-2,5	Н	но	a-butyl	I/cind-a	1207
N(CH <sup>2</sup> CH <sup>3</sup> )			<del>,</del>		
Br_	н	но	ivind-a	n-parkl	9071
	н	но	ıkınq-u	i-pansky	1502
ф-Пиоторантура	Н	но	lysud-a	n-prityi	1504
lγιήzsrэqiq-č	H	HO	η-ρητλί	l/tud-a	1203
+ N(CH <sup>3</sup> ) <sup>3</sup>					
	н	но	a-pntyl	E-butyl	7071

	*	Н	ОН	n-butyl	n-butyl	1219
	O N(CH <sub>3</sub> )			_		
	3-methoxyphenyl	H	ОН	n-butyl	n-butyl	1220
	CO <sub>2</sub> CH <sub>3</sub>	н	ОН	a-butyI	n-butyl	1221
$\neg \neg$	3-methoxyphenyl	H	OH	n-butyl	n-butyl	1222
	phenyl	H	OH	n-butyl	n-butyl	1223
	3-nitrophenyl	H	ОН	n-butyl	n-butyl	1224
	3-methylphenyl	H	OH	ethyl	n-butyl	1225
-	5-piperonyl	Н	OH	n-butyl	ethyl	1226
	4-fluorophenyl	н	OH	n-butyl	n-butyl	1227
	· 2-pyrrolyl	н	OH	n-butyl	n-butyl	1228
	3-chloro-4-hydroxyphenyl	н	ОН	n-butyl	n-butyl	1229
	phenyl	н	OH	n-butyl	n-butyl	1230

1231	n-butyl	n-buryl	ОН	н .	
1232	n-butyl	n-butyl	H	OH	3-thiophenyl
1233	n-butyl	n-butyl	OH	H	Br N(CH <sub>3</sub> )
1234	n-butyl	n-butyl	ОН	н	Br + N(CH <sub>3</sub> )

N(CH³) + 1_					-
	H	но	a-butyl	lytud-a	. 1542
lynadyzodiam-E	H	но	n-butyl	n-buryl	1244
I (CH3)	н	но	u-pntyl	JAng-u	1543
Le Col	н	но	JÆ1nq-a	j.£jnq-u	<b>7</b> 771
3-(dimethylaminomethyl)phenyl	н	но	n-butyl	n-butyl	1741
4-тефоху-3-тефуррету	H	но	a-butyl	n-batyl	1240
Pt.	н	но	υ-ρπέλη	u-pnţλj	6521

_						
		н	но	repression of	a-butyl	8621
13	ī z <sub>i</sub> l					-23.
	(C3)					·
Ŀ	<b>V</b> (`	. н	но	n-prest	Ivind-n	1237
L	4-(bromomethyl)phenyl	Н	HO	a-butyl	n-butyl	1736
	O N(CH <sup>3</sup> CH <sup>3</sup> ) <sup>5</sup>					
ĺ	$\downarrow$	н	но	u-pntyl	u-pntyl	SEZI

1246	n-butyl	n-butyl	OH	H	3-(bromomethyl)phenyl
1247	n-butyl .	n-butyl	ОН	н	ОН
1248	n-butyl	n-butyl	OH .	н	N(CH <sub>3</sub> )
1249	n-butyl	n-butyl	ОН	н	CF <sub>3</sub> CO <sub>2</sub>
1250	p-butyl	n-butyl	OH	Н	3-(dimethylamino)phenyl
1251	n-butyl	n-butyl	OH	Н	1-naphthyl
1252	n-butyl	n-butyl	ОH	Н	1 + H(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>

1253	n-butyl	n-butyl	ОН	Н	N(CH <sub>3</sub> )
1254	n-butyl	n-butyl	ОН	Н	Br +
1255	n-butyl	n-butyl	ОН	н	I- 1- + N(CH <sub>3</sub> ) <sub>3</sub>
1256	n-butyl	n-butyl	OH	H	3-nitrophenyl
1257	n-butyl	n-butyl	OH	Н	phenyl
1258	n-butyl	n-butyl	OH	H	4-fluorophenyl
1259	ethyl	n-butyl	Н	OH	Н
1260	ethyl	n-butyl	OH	H	3-hydroxyphenyl

œ	2
77.7	
Š	
S	2

_						
	0 S 0 N 1					
		н	но	n-butyl	n-parixl	1471
136	Br. Br.	н	но	n-pntλ <sub>l</sub>	1/tind-a	0421
	it to	н	но	I-butyl	n-parkl	6921
	1 Tu(ch <sub>2</sub> ch <sub>3</sub> )					
	~ (\	н	но	lytud-a	Ithud-a	1768

				-(122.72	(07)
S-piperonyl	Н	НО	etbyl	J/Jnq-u	L971
OCH <sup>3</sup>	н	но	lyind-n	μέμης-α	9971
4-fluorophenyl	H	но	I\tinq-a	a-buryl	5971
4-thorophenyl	H	HO	J/mq-α	Iviud-a	1764
fynoradiq-2	Н	НО	υ-ρπίλη	fytud-a	1363
S-thiophenyl	Н	НО	lysud-a .	Period-a	1562
Service of the servic					×
	н	HO	l{thd-a	n-butyl	1971

PCT/US00/02503

1272	n-butyl	n-butyl	• ОН	Н .	I- CO <sub>2</sub> H
1273	n-butyl	n-butyl	OH .	н	I- (CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub> +N—(CH <sub>2</sub> ) <sub>8</sub> CH 3 (CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub>
1274	n-butyl	n-butyl	ОН	Н	CI CI

1275	n-butyl	n-butyl	ОН	н	F 1 + N + + N + + N + + N + + N + + N + + N + + N + + N +
1276	n-butyl	n-butyl	ОН	н	I- (CH <sub>2</sub> ) <sub>6</sub> CH(CH <sub>3</sub> ) <sub>2</sub> + N—(CH <sub>2</sub> ) <sub>6</sub> CH(CH <sub>3</sub> ) 3 (CH <sub>2</sub> ) <sub>6</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
1277	n-butyl	n-butyl	ОН	Н	F

НО	сфАј	jánq-a	1287
но	u-pntyl	lyind-a	1286 1286
HO	n-butyl cthyl	n-butyl	1284
HO		D-pntAj	1283
			7871
			1871
	НО	HO lylud-m	HO Kinq-u IAma

	N(CH <sup>3</sup> ) <sup>2</sup>	н	но	JÆinq-¤	1/sinq-u	1380
667	I- (CH <sup>3</sup> ) <sup>2</sup> CH  (CH <sup>3</sup> ) <sup>2</sup> CH	н	но	ը. - բուչյ	ivind-n	6121
	I- (CH <sup>5</sup> ) <sup>4</sup> CH <sup>3</sup> I- (CH <sup>5</sup> ) <sup>4</sup> CH <sup>3</sup>	н	но	J&inq−0	į Kiną-u	8121

1289	n-butyl	n-butyl	ОН	н	I- (CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> + N—(CH <sub>2</sub> ) <sub>7</sub> CH
1290	p-butyl	n-butyl	OH	н	F HO N +
1291	n-butyl	n-butyl	ОН	н.	CF <sub>3</sub> CO <sub>2</sub>

n-butyl	n-butyl	ОН	н	+ I P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>
n-butyl	n-butyl .	OH		
a-butyl	n-butyl	ОН	н	
	n-butyl	n-butyl n-butyl	n-butyl n-butyl OH	n-butyl n-butyl OH H

90
32
5
₹
-8
=
$\simeq$
>

-fluorophenyl	Н	НО	a-butyl	lytud-a	1302
3-тегрохурьеву!	н	НО	a-butyl	I\frac{1}{2}	1304
Ţ					
O (CH <sup>3</sup> ) <sup>3</sup>	н	но	j∆inq-a	lyind-a	1303
3-һуасаурыстуі	Н	но	Ivind-a	lyind-a	1305
3-тепрохурфену/	H	НО	n-pari	ίζιυς-α	1301
H	но	H	ctbyl	lytud-a	1300
e(CH <sup>3</sup> CH <sup>3</sup> ) <sup>5</sup> +  E 2E3	н	но	г-рицуі	a-buryl	6671
(CH)					
	н	но	n-parky	n-pntyl	1298

143	+ +	н	но	lvind-n	n-pnr,ì	<i>L</i> 671
H	O O N(CH³CH³)	н	но	ηλιπα-α	լásnq-u	9671
	OC(6H2))					
	Br	н	но	lyjud-a	l/tinq-u	1595

1306	n-butyl	n-butyl	ОН	н	O CF <sub>3</sub>
			OH	н	H
1307 1308	n-butyl ethyl	n-butyl n-butyl	OH	<u>н</u>	
1309	n-butyl	n-butyl	ОН	H	4-methoxyphenyl
1310	ethyl	n-butyl	OH	Н	phenyl
1311	n-butyl	ethyl	OH	Н	phenyl
1312	n-butyl	ethyl	ОН	Н	phenyl
1313	n-butyl	ethyl	OH	Н	phenyl
1314	ethyl	n-butyl	OH	H	phenyl
1315	ethyl	n-butyl	OH	Н	phenyl
1316	n-butyl	ethyl	OH	Н	phenyl
1317	n-butyl	ethyl	ОН	H	phenyl

		n-butyl	OH	H	phenyl
1318	ethyl	n-butyl	OH	<del>- H</del>	3-methoxyphenyl
1319	ethyl		OH	— <u>H</u>	phenyi
1320	ethyl	n-butyl	OH	H	phenyl
1321	n-butyl	ethyl	OH	H	
1322	n-butyl	n-butyl	OA	n	
1323	n-butyl	n-butyl	ОН	н	N N N N N N N N N N N N N N N N N N N
1324	n-butyl	n-butyl	ОН	н	1- N+ +
1325	n-butyl	n-butyl	ОН	н	4-((diethylamino)methyl)phenyl
1323	II-Duty1	ii-outy i		<del></del>	1

361	CE <sup>3</sup> CO <sup>3</sup>	н	но	u-pangaj	n-pmλj	IEEI
		н	но	J∕anq-u	Į <b>ć</b> iną-a	OEET

	O T T T T T T T T T T T T T T T T T T T	н	но	u-pniyl	jámq-u .	6 <b>2</b> E1
147	+ N -1 -1			pengag	Į£inq-ti	1358
L	0 0	H	HO HO	n-path(	n-prity!	LZEI
	HO + O O O O O O O O O O O O O O O O O O	**				
		н	но	ivind-a	υ-ραίλι	1356

+ .N(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>

PCT/US00/02503

PCT/US00/02503

	•				
1335	p-butyl	n-butyl	ОН	н	I- N+ N+
1336	n-butyl	n-butyl	OH	Н	I- N N
1337	n-butyl	n-butyl	OH	н	I (H <sub>3</sub> C) <sub>3</sub> N +

n-butyl

n-butyl

1333

1334

n-butyl

n-butyl

n-butyl

H

ОН

ОН

	-N++N++N+++N++++++++++++++++++++++++++					
17.	_I	н	но	D-presky	ս-բու <b>λ</b> լ	1324
57	OE3CO2	н		u-pntyl	j.kjnq-u	esei
	- Br	н	но	լ Հյոգ-ս	[Ámq-u	· <b>2</b> 581

	(CH <sup>3</sup> (CH <sup>3</sup> )(CH <sup>3</sup> ),					
	CF,CO2,					
1		l i				
Ι.	~ (\	н	HO	lytud-a	n-press	1561
	3-Пиото-4-тейохуриспу1	н	но	lytud-a	lytud-a	1350
<u> </u>	рспу	Н	HO	n-butyl	сгрλј	6451
	русилу	Н	но	lytudozi	Igobutyl	8461
<u>a</u> —	3-Цполо-4-шегрохурьспу1	Н	но	lytud-a	lytud-a	<b>L</b> 751
1	рспуј	H	но	a-butyl	ετρλ	1346
_	рустуј	H	но	lyind-a	ethyl	1342
1	3-циоло-4-инсирохурьску	Н	НО	<b>Ι</b> λιπα−α	l/tinq-u	1344
-	руспул	H	но	a-butyl	сक्री	1343
	γ. Αποιοσία-ς	Н	но	lytud-a	a-butyl	1345
- ⊢-	3-тестрохуристу!	Н	acetoxy	lytud-a	Ιγτυά-α	1961
$\vdash$	ς-biperonyl	H	но	ctbyl	α-ρατλ	1340
	С(СНЭ)					
		н	но	ιλιης-α	l/tinq-a	1336
<u> </u>	4-inchoxyphenyi	н	НО	n-butyl	n-butyl	8561

1355	n-butyl	n-butyl	ОН	н .	I-   +   +   +   +   +   +   +   +   +
1356	n-butyl	n-butyl	OH .	H	1 + N
1357	n-butyl	n-butyl	ОН	Н .	F of 3 Br

1358	n-butyi	n-butyl	ОН	н	I- +P(CH <sub>2</sub> CH <sub>3</sub> )
1359	n-butyl	n-butyl	ОН	H	1- N + N

	2HN N + N C -1	н	но	, μέχτιαμα-τα	Į.Kinq-a	<b>₩</b>
156	I. O S N(CH <sub>3</sub> )	н	но	ιένη-υ	ı/snq-u	6961
	HO + N - I	н	НО	Kinq-u	[Amq-u	2961

155		н	но	į∕inq-a	[Kinq-a	1961
	Z	н	но	-parskj	Į∕sinq−u	1260

1365	n-butyl	n-butyl	OH .	H	I- 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
1366	n-butyl	n-butyl	ОН	Н	F + + + + + + + + + + + + + + + + + + +
1367	n-butyl	n-butyl	OH .	н	I- N + N

1368	n-butyl	n-butyl	ОН	H	I- N+ 1
1369	n-butyl	n-buty1	ОН	Н	

		Н	но	J£1nq−u	jKmq-u	SLEI
041	E - O - I	н	но	J <b>Æ</b> jn <b>q</b> −u	jking-a	<del>1</del> /251
	-1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -	н	но	u-pntAį	ηλιης-α	£LE1
-				listed	Intriden	121

		,				
	$\begin{array}{c c} & & & \\ & & \\ & & & \\ & & \\ & & \\ & & & \\ & & \\ & & & \\ & & \\ & & \\ & & & \\ & & \\ & & & \\ & &$	н	но	penis)	[/sinq-a	<b>Z</b> LE1
154	1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	н	но	, <u>Г</u>	n-paşλi	1261
	+ N -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1		но	ı,≤ınq-u	ı/sınq-u	0451

1376	n-butyl	n-butyl	ОН	н	F 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
1377	n-butyl	n-butyl	OH	н	I- + N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1378	n-butyl	n-butyl	ОН	Н .	+ N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1379	n-butyl	n-butyl	OH .	Н	1 + N(CH <sub>2</sub> CH <sub>3</sub> )

1380	n-butyl	n-butyl	ОН	Н	I-
1381	n-butyl	n-butyl	ОН	н	+ N(CH <sub>2</sub> CH <sub>3</sub> )
1382	n-butyl	n-butyl	ОН	н	1-

	Ī	н	но	l\tud-a	υ-ρπίλι	1388
691	L (CH <sup>2</sup> CH <sup>3</sup> ) <sup>3</sup>	н		ս-բուչչյ	p.kjnq-a	<b>८</b> 8६1
	I- (CH <sup>2</sup> CH <sup>3</sup> )					
- 1	<b>/   '</b>	н	но	ը-քում	n-butyl	9851

		н	но	Į∕sinq-a	į/sinq-a	\$881
163						
- 1	j -1	н	но .	լ/փոգ-ա	n-parkl	1384
- 1	·I	н	но	a-butyl	a-butyl	1383

1389	n-butyl	n-butyl	ОН	H	
					I N
1390	n-butyl	n-butyl	ОН	н	
1391	n-butyl	n-butyl	ОН	н	ĭ
					F O V

1392	n-butyl	n-butyl	ОН	Н	<u> </u>
	2)				I- +N
1393	n-butyl	n-butyl	OH	н	I- + HWOLL OLL)
. 1394	n-butyl	n-butyl	ОН	н	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>

	P (CH3)3					
-	£ [ ]	н	но	a-butyl	lytud-a	1400
891	- I - I - I - I - I - I - I - I - I - I					
	· · · · · · · · · · · · · · · · · · ·	н	но .	Iviud-12	lytud-a	1366
	+ N					·
	-1	н	но	It-butyl	lywd-a	8651

_						
	+ Z -1	н	но	г-рагуј	lvind-a	<b>L6</b> E1
7	0 + v(cH <sup>3</sup> cH <sup>3</sup> ) <sup>3</sup>					500.
167	-1					
-		н	но	I-butyl	լՀյոզ-ա	9621
	-I O				· ,	
	<b>+</b>	н	но	ηζιης-α	ս-թուλլ	56E1

1401	n-butyi	n-butyi	OH	Н	F 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
1402	n-butyl	n-butyl	ОН	н	
1403	n-butyl	n-butyl	ОН	Н	1- 0 + 2

1404	n-butyl	n-butyl	ОН	. H	1- 0 N+
1405	n-butyl	n-butyl	ОН	Н	I- CO <sub>2</sub> H
1406	n-butyl	n-butyl	ОН	н	I- N+

-T					·
, 👉	н	но	I/Jaq-u	լՀյոզ-ս	7141
Ph(CH <sup>3</sup> CH <sup>3</sup> )					
_11	н .	но	n-butyl	a-butyl	1101
H <sub>CO2</sub> H		но	լ Հփոգ-ս	µ∕sınq-u	1410

<u> </u>					
To Vichych)	X				
	, н	но	[shnq-tr	n-pntyl	60†1
+ +	н	но	n-butyl	ո-ծաքу!	1408
(CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup> N					
<u> </u>	н	но	υ-ρπέλι	ո-Նուչվ	L07 I

					H + +
1414	n-butyl	n-butyl	ОН	н	1- XH + X

1415	n-butyl	n-butyl .	OH .	H	1-
1416	n-butyl	n-butyl	ОН	н	I-
1417	n-butyl	n-butyl	ОН	Ĥ	+ N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
	-				

3
Ę
È
ō
₹

	н	но	ւչուգ-ս	րերոգ-ս	1761
I I	Н	но	para-a	u-pnrλ	1420

176	C(CH <sub>2</sub> N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub>					
		н	HO.	IVIUG-a	ιζιπο-α	6171
	HO HO OH		4)			
L		н	но	թերդ-ս	IVMG-11	1418

1422	n-butyl	n-butyl	ОН	н	1 + N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
· 1423	n-butyl	n-butyl	ОН	н	H + H
1424	n-butyl	n-butyl	ОН	H	1 +   1   1   1   1   1   1   1   1   1

1425	n-butyl	n-butyl .	ОН	Н	I-
1426	n-butyl	. hutd	ОН	н	+ N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1425	n-outy)	n-butyl	On .	n	I- + N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>
1427	n-butyl	n-butyl	ОН	H	л- О

0	o
1	Ŕ
e	•
3	ς.
5	3
¢	>
3	•
-	

		н	но	a-pniyl	JAinq-u	7641
180	O + (CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup>	н	но	a-patàl	υ-ρειέλן	l E P I
	+ 1					
	ıa Pa	н	но	J⁄sinq-u	Įćinq-u	1430

	•						
129	N(C <sub>6</sub> H <sub>5</sub> )						
		н	но	I√Tud-n	p-park).	1456	
•	HO S						
Į		н	но	u-pntλj	a-butyl	8701	

	n-butyl	n-buryl	ОН	н	F 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
1434	n-butyl	n-butyl	ОН	Н	0 I + N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>

1435	n-butyl	n-butyi	ОН	H	F OH OH
1436	n-butyl	n-butyl	OH	н	
1437	n-butyi	n-butyl	ОН	Н	Br - + P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>

NO ON					
	н	НО	n-pntyl	JÁmq-u	1444
+					
.I	н	но	n-butyl	ա-բուշչլ	1443
CO <sup>5</sup> H					
H <sub>6</sub> Oq -, ¬¬	Н	но	n-butyl	n-butyl	1442

_						
	O + (CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup>	н	но	reprijaj	į kiną-a	1661
183	HO TO			16100 T	, (m. 7	
⊢	8, ,	н	но	lytud-a	I/Jud-a	1440
	+ (CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>	н	но	u-pntλl	a-pniyl	6E <b>≯</b> I
	F(CH <sup>3</sup> CH <sup>3</sup> ) <sup>3</sup>					
L		н	но	ո-եսայի	n-prnAl	1438

1445	n-butyl	n-butyl	ОН	н	SO <sub>3</sub> Na
1446	n-butyl	n-butyl	ОН	н	Br N
1447	n-butyl	n-butyl	ОН	H	Na <sup>+</sup>
1448	n-butyl	n-butyl	ОН	н	F Na <sup>+</sup>

	1440					
	1449	n-butyl	n-butyl	ОН	н	
ı	1450	n-butyl	n-butyl	ОН	н	phenyl
	1451	n-butyl	n-butyl	OH	Ĥ	SO <sub>3</sub> H

 onims-C	Н	671
 7-(O-benzylcarbamato)	н	871
 onims-7	н	LZ1
 (oransetrastyznod-O)-7	Н	971
 noitizeq-8 and 1s		1
+ (CH <sub>3</sub> ) <sub>3</sub>		
 _II	н н	125
7-рехујаштво	н	133
. onims-T	H	771
 onims-7	н	121
7-(O-benzylearbamato)	н	071
7-(O-text-butylearbarnato)	н	611
7-(O-benzylearbanato)	н	811
 7-(O-benzylcarbamato)	H	
 7-(O-benzylearbamato)	н	. 911
 7-(О-белгулсагбаглаго)	H ·	511

onima-7	н	711
onima-7	н	113
Onims-T	Н	112
onims-7	H	111
7-ecetanido	н	011
onims-7	Н	601
7-(hexylamido)	н	108
onims-7	н	L01
(obimatəəsamord-'\')-\(\(\triangle\)	н	901
7-methanesulfonamido	Н	501
7-dimethylamino	н	104
7-trimethylammonium iodide	н	103
notiteoq-7 ath 1s chimethyltammentyth	н	ZOI
HO, M. S.		
ó <sup>0</sup>	н	101
$p^{(R,R)}$	· 18 <sub>0</sub>	Compound Number

PCT/US00/02503

190

WO 00/47568

		<del></del>
131	Н	at the 7-position
	н .	at the 8-position
133	Н	8-(hexyloxy)
		o (majionj)

outure-7		
	НН	786
orime-7	L H	788
ommo-7	H	L87
7-(O-benzykarbamato)	H	786
(onilodqrom-'+)-7	н	784
lydam-f	4-fluoro-phenyl	283
7-methyl	H	787
7-шећућиетарю	Н	187
· yxorbam-7	Н	280
уженьего	н	617
7-пефоху	н	8LZ
7-тепроху	Н	LLZ
oroufi-7	H	9/2
oroufi-7	3-тефоху-ррепу!	SLZ
orouß-7	Н	774
Ozoufi-7	4-tluoro-phenyl	£LZ
omord-7	3-тесьоху-рьепу!	ZLZ
. J-ptomoo	Н	172
улотьуд-7	Н	072
у-тефоху	4-thoro-phenyl	697
yzothom-7	Н	897
7-тетроху	Н	797
Ухотруд-7	н	592
	penyl	T
7-тегроху	3-trifluoro-methyl-	597
уходэш-Г	н	797
λ-ιπεφιοχλ	3-тейоху-распуі	593
Λ·ιστρουλ	H	797
(lyaibüzsen)-7	Н	771
otqsormthom-r (lymbisse-VA-r	H	143
Manus Mudian.	<del>                                     </del>	- LPI
7-тетулистворо	3-шепроху-распу	791
. notitized-V act 12		
HO Position		
John OH		
John John John John John John John John		
John OH OH	Н	139
HO S-4cctoxy	<u>н</u> н	6E1 8Ci
John OH OH		
HO S-received		
HO HO S-received		
HO Se-acceback		
HO CONTRACTOR AS STOCKBOX AS S		
at the 7-position  8-acetoxy  OH  OH  OH  OH  OH  OH  OH  OH  OH  O		
st the 7-position  8-sectoxy  OH  OH  OH  OH  OH  OH  OH  OH  OH  O		
st the 7-position  8-sectoxy  O  O  O  O  O  O  O  O  O  O  O  O  O		
HOW The Procession of the Proc		
HOY Teachory  Sat the 7-position  S-acctoxy  OH  OH  OH  OH  OH  OH  OH  OH  OH  O		
at the 7-position  8-ace to xy  OH  OH  OH  OH  OH  OH  OH  OH  OH  O		
Horizon Andrew Procession Andr		
OH O		
HOH As the T-position of the thirty of the t		
HO Bedeckbay		
HOH As the T-position of the thirty of the t		

7
0
J
2
š
ĕ
9
ĸ
2

290	Н	7-amino
291	н	7-(O-benzylcarbamato)
292	Н	7-amino
293	H	7-benzylamino
294	Н	7-dimethylamino
295	н	7-amino
296	н	7-amino
1000	H	7-dimethylamino
1001	Н	7-dimethylamino
1002	·H	7-dimethylamino
1003	Н	7-dimethylamino
1004	H	7-dimethylamino
1005	н	7-dimethylamino
1006	Н	7-dimethylamino
1007	Н	7-dimethylamino
1008	Н	7-dimethylamino
1009	н	7-dimethylamino
1010	H	· 7-dimethylamino
1011	Н	7-dimethylamino
1012	н	7-dimethylamino; 9-methoxy
1013	н	7-dimethylamino
1014	Н	7-dimethylamino; 9-methoxy
1015	н	7-dimethylamino
1016	н	7-dimethylamino
1017	н	7-dimethylamino
1018	н	7-dimethylamino
1019	Н	7-dimethylamino
1020	Н	7-dimethylamino
1021	н	7-dimethylamino
1022	н	7-dimethylamino
1023	Н	7-dimethylamino
1024	Н	7-dimethylamino
1025	н	7-dimethylamino

1026	H	7-dimethylamino
1027	Н	7-dimethylamino
1028	н	7-dimethylamino
1029	Н	7-dimethylamino
1030	H	7-dimethylamino
1031	н	7-dimethylamino
1032	Н	7-dimethylamino
1033	н	7-dimethylamino
1034	н	7-dimethylamino
1035	н	7-dimethylamino
1036	Н	7-dimethylamino
1037	Н	7-dimethylamino
1038	H	7-dimethylamino
1039	н	7-dimethylamino
1040	Н	7-dimethylamino
1041	Н	7-dimethylamino
1042	Н	7-dimethylamino
1043	Н	7-dimethylamino
1044	Н	7-dimethylamino
1045	Н	7-dimethylamino
1046	н	7-dimethylamino
1047	н	7-dimethylamino
1048	н	7-dimethylamino
1049	H	7-dimethylamino
1050	н	7-dimethylamino
1051	Н	7-dimethylamino
1052	Н	7-dimethylamino
1053	н	7-dimethylamino
1054	н	7-dimethylamino
1055	н	7-dimethylamino
1056	н	7-dimethylamino
1057	н	7-dimethylamino
1058	н	7-dimethylamino

PCT/US00/02503

196

195

WO 00/47568

PCT/US00/02503

WO 00/47568

ommslydtsmib-7	Н	1133
ominstythsmib-7	H	1172
onimaly(thamib-f	н	1711
onimalythamib-7	н	1120
7-dimethylamino	н	6111
7-dimethylamino	н	8111
onimslythonib-T	н	4111
7-dimethylamino	н	9111
7-dimetbylamino	н	SILI
oministy lamino	н	PIII
onimstydamib-7	н	EIII
onimslythamib-7	н	1112
onimslythsmib-7	н	1111
onimslythemib-7	н	1110
onimslythsmib-T	н	6011
orimslyftamib-7	н	8011
onimsly/thamib-7	н	L011
onimelythamib-7	н	9011
onimalythemib-7	н	5011
отіль П-dimethylamino	н	1104
-V-dimethylamino	н	1103
7-dimethylamino	H	2011
orimely/famib-7	н	1011
7-dimethylamino	н	1100
orinnshylamino-7	н	6601
7-dimethykmino	H	8601
orimethylamino	Н	L601
7-dimethylamino	н	9601
7-dimethylamino	н	\$601
onimalythamib-7	н	<del>\$601</del>
7-dimethylamino	H	£601
-7-dimethylamino	н	Z601
·	н	1601

onimalydomib-7	н	0601
orimethylamino-7	н	6801
7-dimethylamino	н	8801
onimelydamib-T	Н	7801
onimslydbamib-f	H	9801
onimstythemin-C	н	2801
ommslyrbsmib-5	Н	₱80I
orinnalythəmib-7	н	1083
7-dimethylamino	Н	1082
onimstyrbamib-T	Н	1801
onimelythomin-7	H	0801
7-dimethylamino	Н	6/01
ominslydamib-7	н	8701
7-dimethylamino	н	. 2201
orimathytamino-√	н	9/01
7-dimethylamino; 9-dimethylamino	н	\$401
7-dimethylamino	н	<b>⊅</b> /01
onimslythamib-7	н	E701
onimstythemib-7	н	2701
. \-\dimethylamino	н	1401
- 7-dimethylamino	н	0/01
9-dimethylamino		
-iorimslythamib-T	н	6901
7-dimethylamino	н	8901
onimalydismib-9	н	L901
orimethylamino	н	9901
7-dimethylamino	н	5901
onimslydd:on-7	н	<b>†901</b>
onimalytham-7	н	1063
onimslythom-7	н	7901
onimslytham-7	н	1901
onimalystamino	н	0901
7-dimethylamino	Н	6501

PCT/US00/	

1124	H	7-dimethylamino
1125	Н	7-dimethylamino
1126	H	7-dimethylamino
1127	H	7-dimethylamino
1128	н	7-dimethylamino
1129	н	9-dimethylamino
1130	H	7-dimethylamino
1131	н	7-dimethylamino
1132	н	7-dimethylamino
1133	Н	7-dimethylamino
1134	н	7-dimethylamino
1135	н	7-dimethylamino
1136	Н	7-dimethylamino
1137	H	9-(2',2'-dimethylhydrazino)
1138	Н	7-dimethylamino
1139	H	7-dimethylamino
1140	н —	7-dimethylamino 7-(2',2'-dimethylhydrazino)
1141	H	7-(2,2-duneinyinydrazmo) 7-ethylmethylamino
1142	н	7-etnytmethylamino 7-dimethylamino
1143	3-fluoro-4-	7-amenylamino 7-dimethylamino
••••	methoxy-phenyl	7-dimethylamino
1144	Н	7-dimethylamino
1145	<del></del>	9-dimethylamino
1146	— <del>II</del>	7-dimethylamino
1147	<del></del>	7-diethylamino
1148	- <del>H</del>	7-dimethylsulfonium, fluoride salt
1149	H H	7-ethylamino
1150	- H	7-ethylamino 7-ethylamino
1151	H H	7-einyimethylamino
1152	H -	
1153	H	7-(ethoxymethyl) methylamino
1154	H	7-methylamino
1155	- H	9-methoxy
1133	n .	7-methyl

1156	H	7-methylmercapto	
1157	Н	7-fluoro;	
1160		9-dimethylamino	
1158	H	7-methoxy	
1159	H	7-dimethylamino	
1160	н	7-diethylamino	
1161	Н	7-dimethylamino	
1162	Н	7-dimethylamino	
1163	Н	7-methoxy	
1164	Н	7-methoxy	
1165	Н	7-trimethylammonium iodide	
1166	Н	7-trimethylammonium iodide	
1167	H.	7-dimethylamino	
1168	н	7-trimethylammonium iodide	
1169	Н	8-dimethylamino	
1170	н	7-ethylpropylamino	
1171	Н	7-directhylamino	_
1172	н	7-methoxy	
1173	Н	7-ethylpropylamino	
1174	Н	7-phenyl	
1175	Н	7-methylsulfonyl	_
1176	Н	9-fluoro	
1177	Н	7-butylmethylamino	
1178	Н	7-dimethylamino	
1179	н	8-methoxy	
1180	н	7-trimethylammonium iodide	
1181	н	7-butylmethylamino	_
1182	н	7-methoxy	
1183	H	7-fluoro	_
1184	н	7-fluoro; 9-fluoro	
1185	H	7-fluoro	
1186	й	7-fluoro; 9-fluoro	
1187	<del></del>	7-methyl	

ommsly.dbsmib-7	н	1549
ominshydramib-T	Н	1748
Onimskytt)-T	н	L\$Z1
7-dimethythamino	н	1246
onimstythamib-7	н	1245
7-(1'-tnethythythzazido)	Н	1244
ommalythamib-7	Н	1243
7-dimethylamino	н	1747
7-dimethylamino	Н	1921
onimslythamib-7	н	1240
O-dimethylamino	н	1539
7-dimentylamino	н	1238
onimalythamib-7	н	1237
orimely/domin-7	Н	1736
7-dimethylamino	н	5621
ommslydsmin-7	н	1234
onimalydismib-7	H	1233
onimslydamib-9	Н	1232
onimalythamib-7	н	1231
orouf]-7		7,00
9-dimethylamino;	. н	1230
onimethylamino	Н	1339
onimalythemin-7		
. ;omord-8	н	8221
View-butylamino	Н	ISSA
omord-7	Н	1556
7-dimethylamino	H	1325
orouft-7	н	1224
onimaly/thom-7		
	н	1333
orinnslydt>-7	н	1333
7-dimethybamino	н	1221
onimslyqorqozi-7	H	0771

7-фітефуватіло	н	1516
9-methylsulfonyl	Н	1218
onimelythemib-7		LIZI
omord-7	н	9171
очдеэтэти үйлэт-6	н	1512
(obimsmollytham-M)-7	н	1714
	шедюху-рьспуј	
7-фільсфурминіпо	-b-orouts-£	EIZI
(omlodqrom-'4)-9	Н	ZIZI
onimalyhtenin-F	н	1211
ommslyntəmib-7	н	1310
7-dimethylphenyl	н	6071
onimaly/hamib-7	н	1208
-Vimely/lamino	H	4021
7-dirachylamino	н	1206
onimalyhtəmib-7	н	1305
7-спедюху	H H	1504
7-(4'-text-butytphenyl)	н	1203
у-тедоху	H	1202
չ-ւսագրչվ	H	1301
onimslythsmib-7	bycu\lambda	1300
V-dimethylamino	Н	1166
У-тпейюху	H H	
(obimemollytham-N)-7	H	8611
7-ижноху	H	L611
7-(4'-methylpiperazin-1-yl)		9611
orinnalyment)-7	H	5611
onimely, the methylamine	н	Þ611
γκοιρόι-7	Н	<u> </u>
έχοιρλη-ζ	н	Z611
omord-7	Н	1611
sbiboi muinommshthrain-7	н	0611
7-trimethylammonium jodice	н	6811
shiboi muimonmalvihamiti-[	н	1188

PCT/US00/02503

1250	H	7-dimethylamino
1251	Н	7-dimethylamino
1252	Н	7-dimethylamino
1253	Н	7-dimethylamino
1254	н	7-dimethylamino
1255	н	7-dimethylamino
1256	н	7-dimethylamino
1257	. н	8-bromo; 7-dimethylamino
1258	н	9-(tert-butylamino)
1259	phenyl	7-dimethylamino
1260	н	7-dimethylamino
1261	н	7-dimethylamino
1262	H .	7-dimethylamino
1263	н	7-bromo
1264	Н	7-isopropylamino
1265	н	9-isopropylamino
1266	Н	7-dimethylamino
1267	Н	7-carboxy, methyl ester
1268	Н	7-dimethylamino
1269	Н	7-dimethylamino
1270	Н	7-dimethylamino
1271	н	7-dimethylamino
1272	Н	7-dimethylamino
1273	H	7-dimethylamino
1274	H -	7-dimethylamino
1275	Н	7-dimethylamino
1276	H	7-dimethylamino
1277	H	7-dimethylamino
1278	H	7-dimethylamino .
1279	H	7-dimethylamino
1280	Н	7-dimethylamino
1281	Н	7-dimethylamino
1282	н	7-trimethylammonium iodide

1283	Н	7-dimethylamino
1284	H	9-ethylamino
1285	н	7-dimethylamino
1286	Н	7-dimethylamino
1287	Н	7-dimethylamino
1288	н	7-dimethylamino
1289	H	7-dimethylamino
1290	Н	7-dimethylamino
1291	H	7-dimethylamino
1292	н	7-dimethylamnio
1293	н	7-dimethylamino
1294	Н —	
1295	H	7-dimethylamino
1296	H	7-dimethylamino
1297	H H	7-dimethylamino
1298	<del>  "</del>	7-dimethylamino
1299	H	7-dimethylamino
1300	phenyi	7-dimethylamino
1301	H	7-dimethylamino
1302	H H	7-trimethylammonium iodide
1303	<del>''</del>	9-hydroxy .
1304	H H	7-dimethylamino
1305	H	7-tert-butylamino
1306	H	9-methylamino
1307		7-dimethylamino
1308	4-methoxy-phenyl	9-(4'-morpholino)
1309	H	7-dimethylamino
1310		9-fluoro
1311	H	7-amino
	Н	7-(hydroxylamino)
1312	H	8-hexyloxy
1313	H	8-ethoxy
1314	Н	7-(hydroxylamino)
1315	Н	7-(hexyloxy)

	onimsly/dramib-7	н	7961
	7-dimetly/lamino	Н	1981
	ominslyhamib-7	Н	1390
	onimslythsmib-7	H	6551
	onimslydtəmib-7	н	85E1
	7-dimehylamino	н	LSEI
	onims/yhamib-7	н	9581
1	orimslythamib-7	н	SSEI
	7-dimethylamino	н	1324
	7-dimenylamino	н	ESEI
	onimelythamin-7	н	ZSEI
	7-dimethylemino	. й	1551
	7-trimethylammonium iodide	н	05E1
	7-dimetlythamino	н	1349
	7-аітейуізтіло	н	1348
	7-dimethylamino	й	1347
1	at the 8-position		
	0 001		ļ
- 1	> \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	н	9951
-	7-primethylammonium iodide	Н н	1346
	omimalythemia-7 sbiboi muinommalythemia-7	Н.	1345
		H H	54£1
	(lyndorouh-'4)-7 - omine-7 ominelythamin-7	Н Н Н	59E1 59E1
	(lyndorouh-'4)-7 - omine-7 ominelythamin-7	Н Н Н Н	1345 1345 1345 1345
	onime-7 onimelythemin-7	н н н н	54E1 54E1 54E1 14E1
	onimalythamib-7 (lynahdqnouli-1»}-X onima-7 onima-7	Н Н Н Н Н	04E1 54E1 54E1 54E1 54E1
	ommskytasmib-7 lytham-7 ommskythamib-7 (lythadqonull-th)-7 ommskythamib-7 ommskythamib-7	H H H H H H	20E1 20E1 20E1 20E1 20E1 20E1
	lytbən-7 onimalythəmib-7 (lyrədqoouli-1»)-7 onima-7 omimalythəmib-7	H H H H H H	\$651 8551 8451 8451 8451 8451 8451
	minnshybrenis-T (i/missipshipsipsipsipshipsipsipshipsipsipshipsipshipsipshipsipshipsipshipsh	H H H H H H H	5 PE 1
	oninskytamia-T  oninskytamia-T  (lyinserapitythamia-Ta-ta-ta-ta-ta-ta-ta-ta-ta-ta-ta-ta-ta-ta	H H H H H H H H H H H H H H H H H H	5PE1 PPC1 EPC1 ZPC1 1PC1 OPC1 6CC1 8EE1 ZCE1 9EE1
	onimslythomb-f onimslythomb-T (lyniseropidlythom-b)-T onimslythom-D-T lythom-C lythom-T onimslythom-b-T onimslythom-F onimslythom-I onimslytho	H H H H H H H	5 PE 1

7-dimethylamino	Н	7551
7-dimethylamino	Н	1881
7-dimethylamino	Н	1330
onimalydamib-7	н	6251
onimslythamib-7	Н	1328
7-dimethylamino	н	LZEI
onimslydiəmib-7	н	1326
onimslyth>mib-7	Н	1372
· onimslythamib-7	Н	1324
onimethylamino-7	Н	1373
oninslylamino	Н	1322
at the 8-position	н	1261
onims-7	H	1320
onfil-T	н	6151 -
onimelyth≎mib-7	н	8161
at the 8-position		
Ţ	н	LIEI
8-руфгоху	11	9161

	Ŧ	
	3	
	2	
į	S	
į	S	
1	Š	
	<b>₩</b>	

1363	н	7-dimethylamino
1364	Н	7-dimethylamino
1365	Н	7-dimethylamino
1366	н	- 7-dimethylamino
1367	н	7-dimethylamino
1368	н	7-dimethylamino
1369	н	7-dimethylamino
1370	Ĥ	7-dimethylamino
1371	Н	7-dimethylamino
1372	н	7-dimethylamino
1373	н	7-dimethylamino
1374	н	7-dimethylamino
1375	н	7-dimethylamino
1376	, н	7-dimethylamino
1377	н	7-dimethylamino
1378	н	7-dimethylamino
1379	Н	7-dimethylamino
1380	H	7-dimethylamino
1381	H	7-dimethylamino
1382	н	7-dimethylamino
1383	H	7-dimethylamino
1384	н	7-dimethylamino
1385	H	7-dimethylamino
1386	H	7-dimethylamino
1387	н	7-dimethylamino
1388	H	7-dimethylamino
1389	Н	7-dimethylamino
1390	Н	7-dimethylamino
1391	Н	7-dimethylamino
1392	H	7-dimethylamino
1393	Н	7-dimethylamino
1394	Н	7-dimethylamino
1395	н	7-dimethylamino

1396	н	7-dimethylamino
1397	Н	7-dimethylamino
1398	Н	7-dimethylamino
1399	H	7-dimethylamino
1400	Н	7-dimethylamino
1401	н	7-dimethylamino
1402	H	7-dimethylamino
1403	Н	7-dimethylamino
1404	Н	7-dimethylamino
1405	н	7-dimethylamino
1406	Н	7-dimethylamino
1407	н	7-dimethylamino
1408	н .	7-dimethylamino
1409	Н	7-dimethylamino
1410	Н	7-dimethylamino
1411	Н	7-dirnethylamino
1412	Н	7-dimethylamino
1413	н	7-dimethylamino
1414	Н	7-dimethylamino
1415	H	7-dimethylamino
1416	Н	7-dimethylamino
1417	Н	7-dimethylamino
1418	н	7-dimethylamino
1419	Н	7-dimethylamino
1420	н	7-dimethylamino
1421	Н	7-dimethylamino
1422	H	7-dimethylamino
1423	Н	7-dimethylamino
1424	Н	7-dimethylamino
1425	н	7-dimethylamino
1426	н	7-dimethylamino
1427	н	7-dimethylamino
1428	Н	7-dimethylamino

PCT/US00/02503

Table 2

odimethylemino
7-dimethylemino

WO 00/47568

PCT/US00/02503

8-O(tio-propyi) 8-SCH3 8-SCH3 8-SCH3 8-SO2CH3 8-SO2CH3 8-SO4CH3 8-NHCH4 8-NHCH3 8-NHCH3 8-NHCH3 8-NHCH3 8-NHCH3 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CO2H 8-NHCH2CH2CO2H 8-NHCH2CH2CO3H 8-NHCH2CH3 1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-	R <sup>1</sup> /R <sup>2</sup>	R³∕R	R <sup>5</sup> /R <sup>6</sup>	(R <sup>X</sup> )q	꿪
				8-O(iso-propyl) 8-SCH <sub>3</sub>	
				8-SOCH <sub>3</sub>	
				8-SCH2CH3	
				8-NH <sub>2</sub>	
				8-NHCH3	
				8-N(CH <sub>3</sub> )2	
				8-N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub> , I	
				8-NHC(O)CH3	
				8-NMeCH2CO2H	
				8-N+(Me)2CH2CO2H,	
				7	
				8-(N)-morpholine	
				8-(N)-azetidine	
				8-(N)-N-	
				methylazetidinium, I"	
				8-(N)-pyrrolldine	
	,			B-(N)-N-meinyi-	
				N-methyl-	
				morpholinium, I'	
				0-(N)-IV-	
				8-(N)-N'-	
				dimethylpiperazinium,	
				S-NH-CRZ	
			٠	8-NHC(0)C4H11	
				8-NHC(0)CH <sub>2</sub> Br	
			-	8-NH-C(NH)NH2	
9-memyi 9-entyi 9-len-propyi 9-len-propyi 9-len-butyi 9-O(Ha-propyi) 9-O(Ha-propyi) 9-SCH3 9-SOCH3 9-SOCH3 9-SO <sub>2</sub> CH3 9-N <sup>+1</sup> (Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H, 1				8-(2)-thiophene	
9-tert-butyl 9-tert-butyl 9-OCH3 9-OCH3 9-OCH3 9-SOCH3 9-SOCH3 9-SOCH3 9-SOCH3 1-				9-methyl	
9-ca-b-propyi 9-ca-b-propyi 9-O(Ha-propyi) 9-S(CHa-propyi) 9-S(CHa-propyi) 9-SOCHa-propyi) 9-SOCHa-propyi) 9-SOCHa-propyi) 1-				9-emyi	
9-OH 9-OCH3 9-OCH3 9-OCH3 9-OCH3 9-SOCH3 9-SOCH3 9-SOCH3 9-SOCH3 1- 1-				9-tert-butyl	
9-OCH <sub>3</sub> 9-O(tto-propyt) 9-O(tto-propyt) 9-SCH <sub>3</sub> 9-SOCH <sub>3</sub> 9-SO <sub>2</sub> CH <sub>3</sub> 9-SO <sub>2</sub> CH <sub>3</sub> 9-N <sup>+</sup> (Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H, I <sup>-</sup>				9-OH	
9-O(16-propyl) 9-SCH3 9-SOCH3 9-SO <sub>2</sub> CH3 9-SO <sub>2</sub> CH3 9-N <sup>+</sup> (Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H, I <sup>-</sup>				9-0СН3	
9-SCH <sub>3</sub> 9-SOCH <sub>3</sub> 9-SO <sub>2</sub> CH <sub>3</sub> 9-N <sup>+</sup> (Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H <sub>1</sub> , I <sup>-</sup>				9-O(iso-propyl)	
9-S0CH <sub>3</sub> 9-S0 <sub>3</sub> CH <sub>3</sub> 9-N <sup>+(</sup> Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H <sub>1</sub> 1"				9-SCH <sub>3</sub>	
9-SO <sub>2</sub> CH <sub>3</sub> 9-N <sup>+</sup> (Me) <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H <sub>1</sub> I				9-SOCH3	
I' Mejichjcojh,				9-502СН3	
				9-N"(Me)2CH2CO2H,	
				-	

ethyl
-propyl

209

찍

Hmethyl
ethyl
n-propyl
n-butyl
n-pentyl
n-hexyl
benzyl

PCT/US00/02503

PCT/US00/02503

WO 00/47568

212

Another class of compounds of particular interest comprises those 1,2consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and benzothiazepines wherein the R1, R2, R3 R4 and R3 radicals are as set forth in group of R\* radicals disclosed in Table 2 above. In one embodiment of the benzyl; and the R\* radical or radicals are independently selected from the Table 3 below; R\* is hydrogen; the R" radical is selected from the group compounds of Table 3, for example, q is 1 and  $R^\chi$  is 7-dimethylamino.

LA mun

Table 3

Compound Number	R¹	R²	R³	R4	R <sup>5</sup>
1452	ethyl	n-butyl	ОН	Н	OH OH
1453	n-butyl	ethyl	ОН	н	ОН
1454	n-butyl	n-butyl	OH	н	ОН

1455	ethyl	n-butyl	ОН	н	NH CO <sub>2</sub> H	
1456	n-butyl	ethyl	. ОН	н	NH CO <sub>2</sub> H	214
1457	a-butyl	n-butyl	OH	н	NH CO,H	

90	
×	
<u>-</u>	
₹	
2	
Ξ	
ي	
⋧	

	· FHNEOS					
216						
1		н	но	n-butyl	o-butyl	1463
	t HN t OS					
	¥	н	но	स्यंग्रे	Ivind-n	7961
	*HN*OS					
		н	но	lyind-a	сџуλј	19+1

	. н <sub>2</sub> 00					
315		н	но	a-butyl	a-butyl	1460
T	H <sub>2</sub> O2					
ļ					9	
L		Н	но	etbyl	lytud-a	1429
	M <sub>E</sub> 03					
						*
1	$ \mathcal{X} $	н	но	[KtmQ-a	ettylj	1428

1464	ethyl	n-butyl	ОН	н	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
1465	n-butyl	ethyl	ОН	Н	0 0-s-Me 0 0	317
1466	n-butyl	n-butyl .	ОН	н	0 - u • 0 - u	

1467	ethyl	n-butyl	ОН	Н	
1468	n-butyl	ethyl	OH	н	
1469	n-butyl	n-butyl	ОН	н	

	0 = 0 = 0	\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-	н	НО	lýing-a	lýsna-a	5241
220	0 ≥ 0 .	\-\_\+	н	но	. <b>c</b> ppλ <i>l</i>	į kiną-a	7/71
		<del>                                      </del>	н	но	· lytud-a	cap's J	£491

-				т	ı	1.
		н	но	r-pankj	l/Jud-a	
219		н	но	сфАј	լՀյոզ-ս	1291
	. o _ i = 0	н	но	Į Ksną-u	сџλן	0.1.71

1476	ethyl	n-butyl	ОН	н	Me-15-0.	
1477	n-butyl	ethyl	ОН	н	Me-13-0.	Š
1478	n-butyl	n-butyl	ОН	н	N°E13	

	1479	ethyl	n-butyl	OH	н	+	7
						Me-15-0	
						N N N N N N N N N N N N N N N N N N N	
ł						Но	
	1480	n-butyi	ethyl	ОН	H		
l						Me—'s—o-	دير
						° N°	
						HO	
L			<u> </u>				

	H <sup>E</sup> O3 O	н	но	I√and-a	сфλן	5871
724	***-0.	н	но	L√31nq-u	ţʎɪnq-u	. 14841
	○	н	но	. еџъл	<b>Ι</b> έλη <b>ς</b> -α	£8 <b>†1</b>

223	o	н	но	Гулц-а	сџај	7487
	OH O O O O O O O O O O O O O O O O O O	н	но	ιλιη-α	Į.Kinq-a	. 1841

1486	n-butyl	ethyl	ОН	н	СО <sub>2</sub> Н	
1487	n-butyl	n-butyl	ОН	Н	ССС,Н	

1488	ethyl	n-butyl	ОН	н		
1489	n-butyl	ethyl	ОН	н	** N	9.7.Y
1490	n-butyl	n-butyl	ОН	Н		- 6

	HN O	н	но	lytud-a	ငေဌာန၂	<b>46</b> 91
228	O N NELS	н	но	υ-ραιλι	lýmá-a	9671
B	E 1 3 N O	н	но	<b>- c p</b> λ <sub>1</sub>	n-pntλi	\$661
	E 1 3 N N E 1 3	н	но	l (Jud-a	сгрλј	1454

Ī	· · · · · · · · · · · · · · · · · · ·				•	[
	H <sup>2</sup> CO <sup>3</sup> H					
227	*	н	но	lywd-a	lLing-u	1493
	н <sup>2</sup> 000 М			·		
	¥	н	но	струј	u-panλן	1492
	H CO2, H					
	. *	н	но	n-patkj	cthyl	16 <b>)</b> [

1498	n-butyl	ethyl	ОН	H	N NH	
1499	n-butyl	n-butyl	ОН	Н	N N N N N N N N N N N N N N N N N N N	229
1500	ethyl	n-butyl	ОН	н	2C1	

1501	p-butyl	ethyi	ОН	н	2C1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
1502	n-butyl	n-butyl	ОН	Н	2C1-
1503	ethyl .	n-butyl	ОН	н	ZC1 He gH Du B n

	M <sub>E</sub> OO O					
١						
L	<u> </u>	н	но	n-butyl	ετρλη	. 60\$1
232	N T T T T T T T T T T T T T T T T T T T	н	но	lVind-a	l⁄sinq-a	8051
	N'N-N					
ı	$\leftarrow$	н	но	capyl	l/hud-a	L0S1

	N N N N N N N N N N N N N N N N N N N	н	но	a-pari}i	сџу	9051
231	#0,	н	но	l∢mq-α	l⁄inq-a	5051
	#0,	н	но		g.ivq-e	<b>+</b> 051

1510	z-butyl	ethyl	ОН	н	о со <sub>2</sub> н	
1511	n-butyl	n-butyl	ОН	н	O CO <sub>2</sub> H	233
1512	ethyl	n-butyl	ОН	Н	H NH <sub>2</sub>	

1513	n-butyl	ethyl	ОН	н	H NH <sub>2</sub>	
1514	n-butyl	n-butyl	ОН	H	H NH <sub>2</sub>	734
1515	ethyl	n-butyl	ОН	н	со з н	
1516	n-butyl	ethyi	ОН	н	CO <sub>2</sub> H	

Г						
	.19	н	но	n-patyl	сфλן	1224
		_				
236	.10					
	<u> </u>	Н	но	n-butyl	n-butyl	1253
						_=
	.10			. **		
		н	но	n-butyl	n-butyl	1222
	.10					
	· •	н	но	I\trud-a	ဌောλງ	1251

	н²оэ—∕о					
		н	но	u-pntλj	n-butyl	0751
	с. H <sub>2</sub> OD —	•				
235		н	но	сгрλј	jkinq-u	6151
	M <sub>E</sub> 03—					
		н	но	lytud-a	сгрλј	8151
	HN O					·
		н	но	lytud-a	บ-คกผ้า	LISI

1525	n-butyl	ethyl	ОН	н	01.	
1526	n-butyl	n-butyl	ОН	н	C C C C C C C C C C C C C C C C C C C	
1527	ethyl	n-butyl	ОН	н	СО <sub>2</sub> Н СО <sub>2</sub> Н	37
1528	n-butyl	ethyl	ОН	Н	CO <sub>2</sub> H	

1529	n-butyl	n-butyl	ОН	н .	СО <sub>2</sub> Н СО <sub>2</sub> Н	
1530	ethyl	n-butyl	ОН	н	o CF,	
1531	n-butyl	ethyl	ОН	н	CF,	
1532	n-butyl	n-butyl	OH	н	o cr.	

	м-соэн	н	но	ငေ့တည် <sub> </sub>	[Kinq-a	1240
240	м <sup>с</sup> со <sup>3</sup> н	н	но	p.pnq.q	сфλլ	6881
	NE CO JH	н	но	ηλίησ-α	ը-թուչվ	8621
	и <sup>2</sup> со <sup>3</sup> и		но	- спАј	l⁄tinq-u	LESI

i	CC 2 M	н	но	ı -pruyl	еџѝј	9651
	**************************************	н	но	l&sud-a	а-рац).	sesi
239	CH	н	но	сџλј	lvind-a	ÞESI
	о — 1- о	н	но	jájng-a	сфλј	EESI

1541	n-butyl	n-butyl	ОН	н		
1542	ethyl	n-butyl	ОН	н	о	
1543	n-butył	ethyl	ОН	н	Со <sub>2</sub> н Со <sub>2</sub> н	74
					о со <sub>2</sub> н	
1544 <sub>.</sub>	n-butyl	n-butyl	ОН	н	Со <sup>2</sup> Н	

1545	ethyl	n-butyl	ОН	Н	R = PEG 1000	
1546	n-butyl	etbyl	OH	н	R = PEG 1000	
1547	n-butyl	n-butyl	ОН	н	R - PEG 1000	242
1548	ethyl	n-butyl	ОН	н	الله الله الله الله الله الله الله الله	

	н	но	сфλј	ĮĄņq-u	8551
	н	но	lytud-a	сџуј	LSSI
244	н	но	lytud-a	a-butyl	9551
	н	но	сџλן	n-pntλſ	SSSI
	n	1.0	14		5551
L	 н	но	Partyl	сдуλј	1224

		н	но	<b>u</b> -pniλj	n-pntλl	1253
		н	но	<b>ε</b> τρλ <u>ι</u> .	u-pntλl	7252
243		н	но	1-pns]	егрλן	1551
	'`\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	н	10	,	i p-butyi	ores
	13~~°\"	н	но	գրութվ	a-butyl	1249

1559	n-butyl	n-butyl	OH	н	THE STATE OF THE S
1560	ethyl	n-butyl	ОН	н	
1561	n-butyl	n-butyl	ОН	н	
1562	n-butyl	n-butyl	ОН	Н	

245

1563	ethyl	n-butyl	ОН	н	
1564	n-butyl	n-butyl	ОН	Н	
1565	n-butyl	n-butyl	ОН	н	346
1566	ethyl	n-butyl	ОН	Н	

•	2
ì	ξ
	Š
3	5
	ξ

		н	НО	u-pntyl	cqrλj	STEI
	EHN N N	н	но	n-pnckj	a-butyl	<b>\$</b> 781
348	EHN H	н	но	сфλլ	n-pritkl	ELSI
	EHM J	н	но	[Ænq-u	сдуу	2,51
	H <sup>2</sup> OO <sup>2</sup> H	н	но	lyzud-a	l⁄sinq-u	

	· · · · · · · · · · · · · · · · · · ·					
	H <sup>E</sup> 03	н	но	сџај	lytud-a	0451
7	H <sub>E</sub> OD W	н	но	kinq-a	cŋλ <u>l</u>	6951
247	_13		-		<del></del>	
		н	но	¡Xmq-a	p.pup.ja	
ļ	· · · · · · · · · · · · · · · · · · ·	п —	no.	panga	hand-n	1368
İ						
L	<b>ス</b>	н	но	сгрλј	n-butyl	<b>1951</b>

1576	n-butyl	ethyl	ОН	Н	
1577	n-butyl	n-butyl	ОН	н	
1578	ethyl	a-butyl	ОН	Н	249
1579	a-butyl	ethyl	ОН	н	

1580	n-butyl	n-butyl	ОН	н	
1560	ir-outy1	L-outy.		**	
1581	ethyl .	n-butyl	OH	Н	M CI
1582	p-butyl	ethyl	ОН	н	H CI
1583	n-butyl	n-butyl	ОН	н	N S N

PCT/US00/02503

WO 00/47568

	H <sup>2</sup> CO <sub>2</sub> H	н	но	сфЛ	ιλιπς-α	. 1651
5.5%	H <sup>2</sup> O3	н	но	1/21nq-12	сгрλן	0651
**	CO <sup>3</sup> H	н	но	Į.⟨inq-ız	a-butyl	. 6851
	со <sup>3</sup> н	н	но	ефλј	þáing-a	8851
		н	но		j£jnq-u	1

_	·					· · · · · · · · · · · · · · · · · · ·
	H <sub>E</sub> 02					
	<u>→</u>	н	но	n-butyl	сфЛј	<i>L</i> 851
	H CO <sup>3</sup> H					
3		н	но	a-butyl	lytud-a	9851
	H CO <sup>2</sup> H					
	<i>★</i>	н	но	сарХј	n-butyl	1282
	H CO <sub>2</sub> H					
	<del>\</del>	н	но	lytud-a	erpkj	<del>+8</del> 51

1592	n-butyl	n-butyl	ОН	н	ССО, Н
1593	ethyl	n-butyl	ОН	н	
1594	n-butyl	n-butyl	ОН	н	
1595	n-butyl	n-butyl	OH	Н	

1596	ethyl	n-butyl	ОН	н	о о о о о о о о о о о о о о о о о о о	
1597	p-butyl	ethyl	ОН	н .	O CO2H	
1598	n-butyl	n-butyi	ОН	н	O S CO 2 H	334
1599	ethyl	n-butyl	ОН	н	CH <sub>3</sub>	

	H <sup>c</sup> os ~ N					
	₹	н	но	n-pathj	a-pntyl	<i>L</i> 091
	H'COS N H H N N N N N N N N N N N N N N N N					
256	<del>\</del>	н	но	cthyl	l\strac-a	9091
	M <sub>c</sub> os N					
		н	но	u-pntλl	ετμλι	\$091
	10 CH3					
1	₹	н	но	1/21nq-u	n-patyl	1604

	· ·					
	CH3 CH3	н	но	<b>द्म</b> ो।	<b>u</b> -pntλj	. 6091
255	CH3	н	НО	n-patyl	сџуλј	1905
	, in	н	но	n-pntyl	n-pntλl	1091
	C1.	н	но	ефλ	n-pntλj	0091

1608	ethyl	n-butyl	OH	н	N S N CO <sub>2</sub> H	
1609	n-butyl	etbyl	ОН	Н	D CO <sub>2</sub> H	
1610	n-butyl	n-butyl	ОН	Н	N CO <sub>2</sub> H	357
1611	ethyl	n-butyl	ОН	н	O SO 3 H	

1612	n-butyl	ethyl	ОН	н	So <sub>3</sub> H
1613	n-butyl	n-butyl	ОН	H	H SO <sub>3</sub> H
1614	ethyl	p-butyl	ОН	н	n=0 or a positive integer
1615	n-butyl	ethyl	ОН	Н	n=0 or a positive integer

	HO HO O HO N H	н	но	укра	γίμη-υ	. 1291
360	HO HO O HO N H N N N N N N N N N N N N N	н	но	, king-u	łyrtiə	1620
	HO HO HO H	н	но	k/thud-n	µ∕\jnq-u	6191

	HO HO HO H	н	но	kyttie	kānd-n	8191
259	HO HO H	н	но	l√rind−a	сфАј	<b>4191</b>
	**************************************	н	но	n-pntyl	[Anq-u	9191

1622	n-butyl	n-butyl	ОН	Ĥ	O OH OH OH
1623	ethyl	n-butyl	ОН	н	он он он
1624	n-butyl	ethyl	ОН	H	он он он

1625	n-butyl	n-butyi	ОН	н	он он он
1626	ethyl .	n-butyl	ОН	н	он он он он он он он
1627	n-butyl	ethyl	OH	н	NO OH OH OH OH

HO ON HO				·	
	н	но	ετρλι	lytud-a	1633
HO OH HO OH	н	но		сгрλј	7632
HO HO OR	н	но	J∕smq-u	J/smq-u	1631
	HO H	HO H	H HO   cdbyl OH H HO OH	а-рагуі а-рагуі он н но н	

	HO HO HO HO	н	но	сџλј	а-рязуј	0691
265	HD HD OH H		но	lçind-a	стрАј	6291
	HO H	н	но	, l/mq-a	Jáing-u	. 8791

1634	n-butyl	n-butyl	ОН	н	но он он он
1635	ethyl	a-butyl	ОН	н	ио он он
1636	n-butyl	ethyl	ОН	н	но — он он он он

1637	n-butyl	n-butyl	ОН	н	+
					но он он
1638	ethyl	n-butyl	ОН	н	<del>-</del>
					он он
1639	n-butyl	ethyl	ОН	н	он он он

	HO OH H	н	но	eqtÀl	l⁄sinq-u	5191
398	HO OH H	н	но	Iguq-u	<b>.</b> εφλ <i>ι</i>	1644
	HO HO HI	н	но	1/sinq-a	p.p.m.d-a	1993

	HO HO HI	н	но	сфАј	lyind-a	1945
267	HO OH H	Н	но	Ivind-a	сфАј	1641
	но он	н	но	n-patàj	1/inq-a	0991

1646	n-butyl	n-butyl	ОН	н		1
					HO CHI CHI	
1647	ethy!	n-butyl	ОН	н	он он	269
1648	n-butyl	ethyl	ОН	н	но — он он он	

1649	n-butyl	n-butyl	ОН	н	он он	
1650	ethyl	n-butyl	ОН	н	HO OH OH	2.70
1651	n-butyl	ethyl	ОН	н	но он он	

271

WO 00/47568

Another group of compounds of interest consists of those compounds of Formula I wherein  $\mathbb{R}^{1}$  and  $\mathbb{R}^{2}$  are alkyl, preferably n-butyl;  $\mathbb{R}^{3}$  is hydroxy; group consisting of amino, dimethylamino and methoxy; and R3 is phenyl R' and R' are hydrogen; R' is hydrogen; R' radicals are selected from the substituted at the para or meta position with one of the following groups: S

2

H

но

l\tud-a

ը-բում

1652

273

274

R = 1000 MW PEG ;

275

WO 00/47568

276

wherein M is selected from the group consisting of Co<sup>a</sup>, Co<sup>a</sup>, Mn<sup>a</sup>, Mn<sup>a</sup>, Fe<sup>a</sup>, Fe<sup>a</sup>, Ni<sup>a</sup>, Ni<sup>a</sup>, Cr<sup>a</sup>, Cu<sup>a</sup>, Zn<sup>a</sup>, Cd<sup>a</sup>, Ga<sup>a</sup>, In<sup>a</sup>, V'', Ru<sup>a</sup>, Pt'', Rh<sup>a</sup> and Ir<sup>a</sup>.

## Dosages. Formulations, and Routes of Administration

The tieal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and/or treatment of hyperlipidemic diseases, conditions and/or disorders by any means, preferably oral, that contacts these compounds with their site of action in the body, for example in the ileum of a mannual such as a human.

2

For the prophylaxis and/or treatment of the diseases, conditions and/or disorders referred to above, the compounds of the present invention can be used as the compound per se. Pharmaceutically acceptable salts are

15 particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts comprise a pharmaceutically acceptable anion or cation. Suitable pharmaceutically

potassium salts, and alkaline earth salts such as magnesium and calcium salts. appropriate include ammonium salts, alkali metal salts such as sodium and medical purposes. Suitable pharmaceutically acceptable base salts where and trifluoroacetic acids. The chloride salt is particularly preferred for citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, appropriate include those salts derived from inorganic acids, such as acceptable acid addition salts of the compounds of the present invention where

S

pharmaceutically acceptable anions such as those anions selected, for example, The anions of the definition of A' in the present invention are 5

ᅜ

by any of the well known techniques of pharmacy, consisting essentially of composition, for example, a tablet or capsule, which can contain from 0.05% or both, and is preferably formulated with the compound as a unit-dose the form of a pharmaceutical composition comprising additional ingredients admixing the components invention. The pharmaceutical compositions of the invention can be prepared substances can also be present, including other compounds of the present to 95% by weight of the active compound. Other pharmacologically active materials are compatible with the other ingredients of the composition and are (collectively referred to herein as "carrier materials"). Acceptable carrier such as acceptable carriers, diluents, excipients, adjuvants and the like deleterious to the recipient. A carrier material can be a solid or a liquid, The compounds of the present invention also can be administered in

20

available for use in conjunction with pharmaceuticals, either as an individual therapeutic compound in a monotherapeutic regimen or as a combination of These compounds can be administered by any conventional means 23

WO 00/47568 PCT/US00/02503

therapeutic compounds in a combination therapy regimen.

administration, and the clinical condition of the recipient compound chosen, the use for which it is intended, the mode of biological effect will depend on a number of factors such as the specific The amount of compound that is required to achieve the desired

single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form bodyweight/day. This total daily dose can be administered to the patient in a bodyweight/day, and more preferably from about 3 to about 10 mg/kg effective to obtain desired results. 100 mg/kg bodyweight/day, preferably from about 1 mg to about 50 mg/kg In general, a daily dose can be in the range of from about 0.3 to about

5

5 more preferably from about 10 to about 50 mg of compound. In the case of benzothiazepine compound, preferably about 1 to about 75 mg of compound pharmaceutically acceptable salts, the weights indicated above refer to the capsules, can contain, for example, from about 0.1 to about 100 mg of weight of the benzothiazepine ion derived from the salt. Orally administrable unit dose formulations, such as tablets or

23 20 physical properties of the formulation, bioadhesion of the dosage form to the release from the dosage form based on the changing pH of the small intestine number of mechanisms. These include, but are not limited to, pH sensitive prolonged or sustained delivery of the drug to the gastrointestinal tract by any invention can include formulations, as are well known in the art, to provide manipulation of the dosage form. Thus, enteric-coated and enteric-coated which the active drug molecule is delivered to the site of action (the ileum) by from the dosage form. The intended effect is to extend the time period over mucosal lining of the intestinal tract, or enzymatic release of the active drug slow crosion of a tablet or capsule, retention in the stomach based on the Oral delivery of an ileal bile acid transport inhibitor of the present

PCT/US00/02503

279

controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

When administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight, and more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an

infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, and preferably from about 1 mg to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

2

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active

23

WO 00/47568

PCT/US00/02503

280

compound(s) and the carrier material (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier material, or both, and then, if necessary, shaping the

- product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface
  - 10 active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent

Pharmaccutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

13

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutancous, intranuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable

25 compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional

WO 00/47568 PCT/US00/02503

resulting mixture. solid carrier materials, for example, cocoa butter, and then shaping the

aerosol, or oil. Carrier materials that can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The w/w of the composition, for example, from 0.5 to 2%. active compound is generally present at a concentration of from 0.1 to 15% skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, Pharmaceutical compositions suitable for topical application to the

ᅜ 5 A suitable concentration of the active compound is about 1% to 35%, as described in Pharmaceutical Research, 3(6), 318 (1986). be delivered from the patch by electrotransport or iontophoresis, for example, preferably about 3% to 15%. As one particular possibility, the compound can compositions suitable for transdermal administration can be presented as the recipient for a prolonged period of time. Such patches suitably contain a solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. compound of the present invention in an optionally buffered, aqueous discrete patches adapted to remain in intimate contact with the epidermis of Transdermal administration is also possible. Pharmaceutical

20 vary depending upon the host treated and the particular mode of the carrier materials to produce a single dosage form to be administered will In any case, the amount of active ingredient that can be combined with

in normal practice, additional substances other than inert diluents, e.g., such as sucrose, lactose, or starch. Such dosage forms may also comprise, as compounds of the present invention admixed with at least one inert diluent tablets, pills, powders, and granules noted above comprise one or more and pills, the dosage forms may also comprise buffering agents. Tablets and lubricating agents such as magnesium stearate. In the case of capsules, tablets, The solid dosage forms for oral administration including capsules,

દ્ધ

WO 00/47568 PCT/US00/02503

pills can additionally be prepared with enteric coatings

compositions may also comprise adjuvants, such as wetting agents clixirs containing inert diluents commonly used in the art, such as water. Such pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and emulsifying and suspending agents, and sweetening, flavoring, and perfuming Liquid dosage forms for oral administration can include

ដ 5 employed including synthetic mono- or diglycerides. In addition, fatty acids solvent or suspending medium. For this purpose any bland fixed oil may be solution. In addition, sterile, fixed oils are conventionally employed as a suitable dispersing or setting agents and suspending agents. The sterile such as oleic acid find use in the preparation of injectables. may be employed are water, Ringer's solution, and isotonic sodium chloride a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that injectable preparation may also be a sterile injectable solution or suspension in oleaginous suspensions may be formulated according to the known art using Injectable preparations, for example, sterile injectable aqueous or

foregoing and the like. Pharmaceutically acceptable carrier materials encompass all the

20

## Treatment Regimen

23 blood levels with the compounds and/or compositions of the present invention disease, the route of administration, pharmacological considerations such as weight, sex, diet, and medical condition of the patient, the severity of the is selected in accordance with a variety of factors. These include the type, age, disease, condition and/or disorder relating to hyperlipemia, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or The dosage regimen to prevent, give relief from, or ameliorate a

PCT/US00/02503

283

the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore

deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or

eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum cholesterol levels by any of the methods well known in the art, to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of iteal bile acid transport inhibitor of the present invention which exhibits satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.

The following non-limiting examples serve to illustrate various aspects of the present invention.

## Examples of Synthetic Procedures

23

The starting materials used in the preparation of the compounds of the following examples, as well as other compounds of the present invention, are commercially available or can be prepared by conventional methods known to one of ordinary skill in the art or in an analogous manner to conventional

WO 00/47568

PCT/US00/02503

284

methods described in the art. The starting materials of the following examples were obtained from commercial sources unless otherwise noted. The ethyl 2-amino-2-butylhexanoate hydrochloride used below was prepared in an analogous manner to the literature method of Stork (J. Org. Chem. 41, 3491

Example 1

(1976)).

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

Step 1. 2-Amino-2-butylhexanol

•

2

To a solution of 29.75 g (0.12 mol) of ethyl 2-amino-2-butylhexanoate hydrochloride in 100 mL of terrahydrofuran cooled to -20 °C was added 148.8 mL of a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran while

- sulfate and concentrated. The resulting yellow oil was dissolved in 300 mL of then brine (300 mL). The ethyl acetate layer was dried over magnesium acetate. The ethyl acetate solution was washed with water (2x200 mL) and temperature. The resulting slurry was filtered and washed with 100 mL ethyl The reaction mixture was stirred for one hour and warmed to room
- ö tetrahydrofuran and concentrated to give 20.61 g of 2-amino-2-butylhexanol as an oil.

Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-fluorobenzenesulfonamide

chloride in 150 mL of tetrahydrofuran was added 36.4 mL of triethylamine. To a solution of 16.95 g (0.09 mol) of 4-fluorobenzene sulfonyl

ᅜ

was washed with water (2  $\times$  200 mL) and brine (300 mL). The ethyl acetate [1-butyl-1-(hydroxymethyl)pentyl]-4-fluorobenzenesulfonamide as an oil. layer was dried over magnesium sulfate and concentrated to give 29.47 g of Nat room temperature. The reaction mixture was concentrated and then the added. The reaction mixture was stirred 30 minutes at 0 °C and then 16 hours 2-butylhexanol (prepared in step 1 above) in 70 mL of tetrahydrofuran was The reaction mixture was cooled to 0 °C and a solution of 19.61 g of 2-aminoresidue was dissolved in 250 mL of ethyl acetate. This ethyl acetate solution

20

WO 00/47568 PCT/US00/02503

286

Step 3. N-(1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino) benzenesulfonamide

as an solid. dimethylamine was prepared and placed in a bomb. The reaction mixture was N-[1-butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)benzenesulfonamide heated to 110 °C for 16 hours, cooled, and then concentrated to give 25.46 g of above, 872 mL of 2.0 M dimethylamine in tetrahydrofuran and 100 mL of neat A solution containing 28.89 g (0.09 mol) of the oil prepared in Step 2

5 4-(dimethylamino)benzenesulfonamide Step 4. N-[1-Butyl-1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-

The ethyl acetate solution was washed with 5% hydrochloric acid solution (2 x prepared in Step 3 and then 14.01 g of imidazole. The reaction mixture was stirred 3 days and then diluted with 1 L of ethyl acetate and 500 mL of water.  $158\ mL$  of dimethylformamide was added  $24.46\ g$  (0.07 mol) of the solid To a solution of 15.51 g (0.10 mol) of t-butyldimethylsilyl chloride in

2

PCT/US00/02503

287

200 mL), water (200 mL) and then brine (200 mL). The ethyl acetate layer was dried with magnesium sulfate and concentrated to an oil. The oil was stirred with hexane and the resulting solid was filtered to give 25.31 g of N-[1-butyl-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)benzenesulfonamide as a white solid.

Step 5. N-[1-Butyl-1-[[[(1,1dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-N-methylbenzenesulfonamide

To a solution of 0.476 g (11.90 mmol) of 60% sodium hydride dispersion in mineral oil in 43 mL of tetrahydrofuran was added 4.0 g (8.50 mmol) of the solid prepared in Step 4 above and then 1.6 mL of dimethyl

으

sulfate dropwise. The reaction mixture was heated at reflux for one hour, cooled to 0 °C, and then water was added. The reaction mixture was concentrated and 250 mL ethyl acetate and 250 mL water added. The layers were separated and the ethyl acetate solution was washed with 1 M

hydrochloric acid (2 x 200 mL), saturated sodium bicarbonate (2 x 200 mL), water (200 mL) and then brine (200 mL). The ethyl acetate layer was dried over magnesium sulfate and concentrated to give 4.63 g of a residue. The residue was purified by flash chromatography with 15% ethyl acetatehexane as cluent to give 3.35 g of M-[1-butyl-1-[[[(1,1dimethylethyl)] dimethylsily]] oxy]methyl]pentyl]4-{dimethylamino}-M-methylbenzenesulfonamide as an

WO 00/47568

PCT/US00/02503

288

Step 6.

To a solution of 3.35 g (6.90 mmol) of the oil prepared in Step 5 above in 35 mL of tetrahydrofuran cooled to 0 °C was added dropwise 9.66 mL of 1.6 M n-butyllithium in hexanes. The reaction mixture was stirred 30 minutes at 0 °C, warmed to room temperature, and stirred one hour. To the reaction mixture was added 6.5 mL of 5% hydrochloric acid and then the Tetrahydrofuran was evaporated. To the residue was added 200 mL dichloromethane and 200 mL water and the layers separated. The dichloromethane layer was washed with brine (200 mL), dried over

Step 7. N-[1-Butyl-1-[I[(1-dimethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide

magnesium sulfate and concentrated to give 3.12 g of a yellow solid.

2

To a solution of 130 mg (0.11 mmol) of tetrakis(triphenylphosphine) palladium(0) in 10 mL of toluene was added 825 mg of 3-nitrobenzyl

289

bromide. After the toluene solution was stirred 10 minutes, a degassed solution of 2.02 g (3.82 mmol) of the solid prepared in Step 6 above in 8 mL ethanol was added followed by 10 mL of 1 M sodium carbonate. The reaction mixture was heated at reflux 45 minutes and then cooled and concentrated. To

the residue was added 250 mL of ethyl acetate. The ethyl acetate mixture was washed with brine (2 x 200 mL), dried over magnesium sulfate and concentrated to give 2.76 g of a residue. To the residue was added 200 mL of 30% ethyl acetate in hexane, and the mixture was stirred 1.5 hours and then filtered through silica. The ethyl acetate solution was concentrated to give 2.30 g of N-[1-būtyl-1-{[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-([3-nitrophenyl)methyl]-N-methylbenzenesulfonamide

5

Step 8. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide

above in 10 mL of tetrahydrofuran cooled to 0 °C was added 4.4 mL of 1 M tetrahutylammonium fluoride in tetrahydrofuran. The reaction mixture was stirred 15 minutes at 0 °C and then 12 hours at room temperature. To the reaction mixture was added 250 mL of ethyl acetate. The ethyl acetate solution was washed with water (200 mL) and brine (200 mL). The ethyl

WO 00/47568 PCT/US00/02501

290

acetate layer was dried over magnesium sulfate and concentrated to give 1.88 g of a brown oil residue. The residue was purified by flash chromatography with 30% ethyl acetate in hexane as eluent to give 1.49 g of N-[1-butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide as a yellow oil.

Step 9. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl) methyl]-N-methylbenzenesulfonamide.

To a solution of 1.49 g (2.95 mmol) of the oil prepared in Step 8 above in 10 mL of dimethylsulfoxide was added 1.23 mL of triethylamine and then 1.41 g of sulfur trioxide pyridine complex. The reaction mixture was stirred one hour and then diluted with 200 mL water. The aqueous mixture was washed with ethyl acetate (3 x 100 mL). The combined organic layers were washed with 5% hydrochloric acid (100 mL) and brine (100 mL). The ethyl acetate layer was dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography with 25% ethyl acetate in hexane as eluent to give 1.31 g of N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide as a yellow oil.

Step 10. (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

PCT/US00/02503

291

To a solution of 504 mg (2.60 mmol) of the oil prepared in Step 9 above in 50 mL of tetrahydrofuran cooled to 0 °C was added 2.80 mL of 1 M potassium t-butoxide in tetrahydrofuran. The reaction mixture was stirred for 15 minutes, water was added, and then the mixture was concentrated to yield a residue. The residue was dissolved in 100 mL ethyl acetate. The ethyl acetate solution was washed with water (100 mL) and brine (100 mL). The ethyl acetate layer was dried over magnesium sulfate and concentrated to give 1.25 g of a semi-solid. The residue was purified by crystallization with ethyl acetate and hexane to give 737.5 mg of (4R,5R)-3,3-dibutyl-7.

(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide as a yellow crystalline solid. <sup>1</sup>H NMR (CDCl,) 6 0.90-1.00 (m, 6H), 1.05-1.80 (m, 12H), 2.50-2.60 (m, 1H), 2.79 (s, 6H), 2.85 (s, 3H), 4.09 (d, J= 9.0 Hz, 1H), 5.76 (d, J= 2.0 Hz, 1H), 5.88 (s, 1H), 6.53 (dd, J= 2.4, 8.9 Hz, 1H), 7.59 (t, J= 7.9 Hz, 1H), 7.84-7.88 (m, 2H), 8.22 (dd, J= 1.0, 8.1 Hz, 1H), 8.47 (s, 1H). MS (M+H') 504.

2

#### Example 2

~

(4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide

WO 00/47568

PCT/US00/02503

23

A solution of 737 mg (1.46 mmol) of the solid prepared in Step 10 of Example 1 was dissolved in 110 mL of ethanol in a 3 oz. Fisher/Porter vessel, and about 150 mg of 10% Pd/C catalyst was added. This mixture was hydrogenated at 40 psi H<sub>2</sub> for 20 hours and then filtered. The filtrate was

- 5 concentrated to give 0.82 g of a semi-solid material. The semi-solid material was crystallized from ethyl acetate and hexane to give 0.51 g of (4K,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrabydro-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide as colorless crystals. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 6 0.89 (t, J=6.6 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H), 1.10-1.45 (m, 8H), 1.60-1.75 (m, 3H), 1.98-2.10 (m, 1H), 2.48-2.58 (m, 1H), 2.79 (s, 6H), 2.81 (s, 3H), 3.69 (s, 2H), 4.12 (d, J=7.8 Hz, 1H), 5.62 (s, 1H), 6.07 (d, J=2.1 Hz, 1H), 6.46 (dd, J=2.4, 8.7 Hz, 1H), 6.61 (br d, J=7.8 Hz, 1H), 6.80 (br s, 1H), 6.89 (br d, J=2.1 Hz, 1H), 7.15 (t, J=7.8 Hz, 1H), 7.79 (d, J=8.7 Hz, 1H), MS (M+H<sup>\*</sup>) 474.
- Example 3

13

5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]pentanamide

To a solution of 0.25 g (0.53 mmol) of the solid prepared in Example 2

- mL). The ethyl acetate layer was dried over magnesium sulfate and  $\times$  25 mL), saturated sodium bicarbonate solution (2 x 25 mL) and brine (25 The combined ethyl acetate layers were washed with 5% hydrochloric acid (2
- 5 [3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2crystallization with ethyl acetate and hexane to give 202.3 mg of 5-bromo-Nconcentrated to give 0.29 g of a solid. The solid was purified by
- 1H), 5.69 (s, 1H), 5.97 (s, 1H), 6.47 (dd, J = 2.4, 8.9 Hz, 1H), 7.24-7.40 (m, solid. 'H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 6.9 Hz, 3H), methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]pentanamide as a tan 1H), 2.78 (s, 6H), 2.81 (m, 3H), 3.41 (t, J = 6.3 Hz, 2H), 4.10 (d, J = 8.5 Hz, 1.20-1.42 (m, 8H), 1.57-2.10 (m, 8H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.46-2.57 (m,

2

4H), 7.76 (br s, 1H), 7.80 (d, J=8.7 Hz, 1H). MS (M+H') 636, 638.

methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-

oxo-pentanaminium trifluoroacetate

20

PCT/US00/02503

294

5 with the product. MS (M') 657: oxo-pentanaminium trifluoroacetate as a white solid. 1H NMR was consistent methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5reaction mixture was concentrated to form a residue. The residue was purified by reverse phase high pressure liquid chromatography to give 16.2 mg of 5mixture was heated at 55 °C for 28 hours and then at 75 °C for 16 hours. The above in 1 mL of acetonitrile was added 87  $\mu$ L of triethylamine. The reaction To a solution of 100 mg (0.16 mmol) of the solid prepared in Example 3 [[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-

hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]acetamide 2-chloro-N-[3-[(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-

PCT/US00/02503

295

To a solution of 100 mg (0.21 mmol) of the solid prepared in Example 4 above in 2 mL of tetrahydrofuran was added 29 mg of bromoacetic acid, 29 µL of triethylamine, and then 40 mg of

- ethyldimethylaminopropylcarbodiimide hydrochloride. The reaction mixture was stirred 16 hours and then 50 mL ethyl acetate was added. The ethyl acetate solution was washed with water, 5% hydrochloric acid (2 x 25 mL), saturated sodium bicarbonate solution (2 x 25 mL), and then brine (25 mL). The ethyl acetate layer was dried over magnesium sulfate and then
- 10 concentrated to give 88 mg of an oil. The oil was purified by flash chromatography with 50% ethyl acetate in hexane as eluent to give 72.0 mg of cis-3,3-dibutyl-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-7-dimethylamino-5-(3-(2-chloroaceamido)phenyl)-1,2-benzothiazepine with a trace of 2-chloro-N-[3-(44,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-
- 15 methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]acetamide present. ¹H NMR was consistent with the product. MS (M+H\*) 550.

WO 00/47568

296

PCT/US00/02503

Example 6

2-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino]-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-2-oxoethanaminium chloride

To a mixture of 63 mg (0.12 mmol) of the material prepared in Example 5 above in 1 mL of tetrahydrofuran was added 64 μL of triethylamine. The reaction mixture was heated to reflux for three days and then concentrated. The residue was triturated with ether to give 66.5 mg of 2[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino]-2,3,4,5-tetrahydro-4-hydroxy-2methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-2oxoethanaminium chloride as a tan solid. <sup>1</sup>H NMR was consistent with the

Example 7

product. MS (M\*) 615.

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

15 methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide

PCT/US00/02503

297

Step 1. N-[1-Butyl-1-[[[(1-dimethylethyl)dimethylsily]]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-methylbenzenesulfonamide

To a solution of 1.00 g (2.06 mmol) of the material from Step 5 of Example 1 above in 10 mL of tetrahydrofuran cooled to 0 °C was added 2 mL of 1.6 M n-butyllithium in hexanes. The reaction mixture was stirred one hour at 0 °C. To the reaction mixture was added 480 µL of trimethyl borate and the mixture stirred 15 minutes at 0 °C and then one hour at room temperature. The reaction mixture was concentrated to form a residue. The residue was dissolved in 20 mL of toluene and 2.1 mL of 2 M aqueous sodium carbonate.

5

WO 00/47568

PCT/US00/02503

270

To the mixture was added 300 µL of p-methoxybenzyl chloride and then 71 mg of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was heated at 100 °C for 16 hours, cooled, and then 50 mL of toluene added. The reaction mixture was washed with water (50 mL) and brine (50 mL), filtered through silica, and concentrated to form a residue. The residue was purified by flash chromatography to give 0.82 g of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-methylbenzenesulfonamide as an oil.

Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(4-10 methoxyphenyl)methyl]-N-methylbenzenesulfonamide

The procedure of Step 8 of Example 1 above was followed except that N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsityl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-methylbenzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsityl]oxy] methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-

5

methylbenzenesulfonamide.

PCT/US00/02503

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl) methyl]-N-methylbenzenesulfonamide

The procedure of Step 9 of Example 1 above was followed except that · N-[1-butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(4-

methoxyphenyl)methyl]-N-methylbenzenesulfonamide was used in place of N-[1-butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(3nitrophenyl)methyl]-W-methylbenzenesulfonamide.

Step 4. (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide

- methoxyphenyl)methyl]-N-methylbenzenesulfonamide was used in place of N-The procedure of Step 10 of Example 1 above was followed except [1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-Nthat N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(4methylbenzenesulfonamide. 2
- 4.10-41.6 (m, 1H), 5.70 (s, 1H), 5.99 (s, 1H), 6.52 (s, 1H), 6.93 (d, J = 8.6 Hz, 14 NMR (CDCl,) 8 0.83-0.96 (m, 6H), 1.15-1.38 (m, 6H), 1.69-1.83 (m, 4H), 2.00-2.08 (m, 1H), 2.55-2.59 (m, 1H), 2.81 (s, 6H), 2.83 (s, 3H), 3.84 (s, 3H), 2

WO 00/47568

PCT/US00/02503

2H), 7.43 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.6 Hz).

Example 8

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4hydroxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide

300  $\mu L$  of boron tribromide. The reaction mixture was stirred for one hour at -To a solution of 0.52 g (1.06 mmol) of the solid prepared in Step 4 of Example 7 above in 10 mL of dichloromethane cooled to -78 °C was added

- tetrahydro-5-(4-hydroxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide 4.12 (d, J=8.0 Hz, 1H), 4.88 (br s, 1H), 5.69 (s, 1H), 6.07 (d, J=2.2 Hz, 1H), concentrated to give 0.46 g of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-1.76 (m, 4H), 2.00-2.10 (m, 1H), 2.51-2.59 (m, 1H), 2.83 (s, 6H), 2.84 (s, 9H), 78 °C and then 100 mL of water and 100 mL of dichloromethane were added. as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 0.82-0.97 (m, 6H), 1.15-1.40 (m, 6H), 1.67-6.60 (dd, J=2.2, 8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.3 Hz, carbonate(100 mL), 10% hydrochloric acid (100 mL) and brine (100 mL). The dichloromethane solution was washed with 10% aqueous sodium The dichloromethane layer was dried over magnesium sulfate and 2 2
- 2H), 7.85 (d, J = 8.6 Hz). HRMS (ES) Calc'd for CaHy, NyO, S: 475.2631. ೫

PCT/US00/02503

301

ample 9

Found: 475.2649.

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-(((2-iodoethyoxy)ethoxy)ethoxy)phenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-

To a solution of 0.38 g (0.80 mmol) of the solid prepared in Example 8 in 8 mL dimethylformamide was added 44 mg of 95% sodium hydride and then 730 μL of 1,2-bis(2-iodocthoxy)ethane. The reaction mixture was stirred one hour. To the reaction mixture was added 100 mL of water and 100 mL of ethyl acetate and the reaction mixture extracted with ethyl acetate. The ethyl acetate layer was washed with brine (100 mL), dried over magnesium sulfate and concentrated to form a residue. The residue was purified by flash chromatography with 10-25% ethyl acetate in hexane as eluent to give 0.37 g of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-(((2-

5

15 iodoethyoxy)ethoxy)ethoxy)phenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide as a solid. HRMS (ES) Calc'd for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>SI: 717.2434. Found: 717.2419. <sup>1</sup>H NMR is consistent with the structure of the product.

WO 00/47568 PCT/US00/02503

302

#### Example 10

1-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethyl]pyridinium

A solution of 75 mg of the solid prepared in Example 9 above in 5 mL of pyridine was heated at 70 °C for 16 hours. The reaction mixture was concentrated to form a residue. The residue was triturated with ether to give 56.8 mg of 1-[2-[2-[4-[(4R,5R)-3,3-dibuty]-7- (dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazzpin-5-yl]phenoxy]ethoxy]ethoxy]ethyl]pyridinium as a solid. ¹H NMR (CDCl<sub>3</sub>) δ 0.89-0.97 (m, 6H), 1.19-1.40 (m, 6H), 1.70-1.74 (m, 4H), 2.00-2.10 (m, 1H), 2.60-2.69 (m, 1H), 2.80 (s, 6H), 2.83 (s, 3H), 3.69-3.72 (m, 4H), 3.83-3.87 (m, 2H), 4.09-4.15 (m, 5H), 5.23-5.27 (m, 2H), 5.70 (s, 1H), 5.97 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 2.4, 8.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.96-8.01 (m, 2H), 8.63-8.67 (m, 2H), 9.52 (d, J = 6.0 Hz, 1H). HRMS (ES) Calc'd for C<sub>3</sub>,H<sub>3</sub>,M<sub>3</sub>O<sub>3</sub>S: 668.3733. Found:

7568

PCT/US00/02503

303

Example 11

2-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-bertzothiazzpin-5-y]phenoxy]ethoxyJethoxyy-N.N.N-triethylethanaminium iodide

The procedure of Example 10 was followed except that triethylamine was used in place of pyridine and heating was at 90 °C for 6 hours. 'H NMR is consistent with the desired product. 'H NMR (CDCI<sub>3</sub>) 8 0.90-0.97 (m, 6H), 1.12-1.45 (m, 15H), 1.60-1.73 (m, 4H), 2.09-2.11 (m, 1H), 2.52-2.55 (m, 1H), 2.82 (s, 6H), 2.83 (s, 3H), 3.06-3.15 (m, 2H), 3.53 (q, J=7.2 Hz, 6H), 3.74-10 3.75 (m, 4H), 3.86-3.89 (m, 2H), 4.04-4.16 (m, 5H), 5.70 (s, 1H), 5.98 (m, 1H), 6.50 (d, J=3.0 Hz, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.7 Hz, 2H), 7.83 (d, J=8.7 Hz, 1H). HRMS (ES) Calc'd for C<sub>11</sub>H<sub>44</sub>N<sub>1</sub>O<sub>6</sub>S: 690.4516. Found: 690.4548.

Example 12

15 (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide

WO 00/47468

PCT/US00/02503

3

The procedures set forth in Example 1 above were followed except that 3-methoxybenzyl chloride was substituted for 3-nitrobenzyl chloride. 'H NMR was consistent with the product. 'H NMR (CDCI,) & 0.90-0.97 (m, 6H), 1.17-1.38 (m, 8H), 1.69-1.73 (m, 2H), 2.04-2.08 (m, 1H), 2.55-2.62 (m, 1H), 2.81 (s, 6H), 2.84 (s, 3H), 3.82 (s, 3H), 4.15 (d, J= 7.8 Hz, 1H), 5.72 (s, 1H), 6.01 (d, J= 2.4 Hz, 1H), 6.50 (dd, J= 2.4, 8.4 Hz, 1H), 6.86-6.89 (m, 1H), 7.05 (br s, 1H), 7.13-7.16 (m, 1H), 7.32 (t, J= 8.1 Hz, 1H), 7.83 (d, J= 8.7 Hz, 1H). MS (M+H') 489.

30S

(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide and (4S,5R)-3,3-dibutyl-7-

(dimethylamino)-2-[(3-nitrophenyl)methyl]benzenesulfonamide Step 1. N-[1-Butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-

mL of  $1.6\,\mathrm{M}$  n-butyllithium in hexane. The reaction mixture was stirred at 0°C for 30 minutes. To the reaction mixture was added 1.9 mL of trimethyl Example 1 above in 10 mL of tetrahydrofuran cooled to 0 °C was added 8.0 To a solution of 2.0 g (4.25 mmol) of the material prepared in Step 4 of

5

WO 00/47568

ᅜ 5 chromatography to give 1.72 g of N-[1-butyl-1-[[[(1and concentrated to form a residue. The residue was purified by flash and brine (100 mL). The ethyl acetate layer was dried over magnesium sulfate of ethyl acetate. The ethyl acetate solution was washed with water (100 mL) for 16 hours. The reaction mixture was concentrated and dissolved in 100 mL nitrobenzaldehyde. The ethanol solution was added to the toluene solution to form a residue. The residue was dissolved in 7 mL of ethanol and degassed and the solution extracted. The ethyl acetate layer was washed with water hydrochloric acid to bring the solution to a pH of 6-7 and then the volatiles dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3followed by 10 mL of 1 M aqueous sodium carbonate. The reaction mixture tetrakis(triphenylphosphine)palladium(0), 10 mL of toluene and 918 mg of 3with nitrogen. In a separate flask was placed 150 mg of (100 mL) and brine (100 mL), dried over magnesium sulfate and concentrated were evaporated. To the aqueous solution was added 100 mL of ethyl acetate borate and the mixture stirred 10 minutes at 0 °C and then one hour at room was heated to reflux for one hour, cooled to room temperature, and then stirred temperature. To the reaction mixture was added 100 mL of water and 5%:

20 Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(3nitrophenyl)methyl]benzenesulfonamide

nitrophenyl)methyl]benzenesulfonamide.

307

The procedure of Step 8 of Example 1 was followed except that N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4 (dimethylamino)-2-[(3-nitrophenyl)methyl]benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4 (dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide.

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl) methyl]benzenesulfonamide

To a solution of 79 μL of oxalyl chloride in 2 mL of dichloromethane cooled to -78 °C was added 107 μL of dimethylsulfoxide and the mixture stirred 20 minutes. To the cooled reaction mixture was added a solution of 370 mg (0.75 mmol) of the alcohol from Step 2 above in 2 mL of dichloromethane and the mixture was stirred one hour at -78 °C. To the cooled reaction mixture was added 660 μL of diisopropylethylamine. The reaction mixture was warmed to room temperature and stirred for 30 minutes. To the reaction mixture was added 100 mL of water and mixture was extracted with dichloromethane (2 x 50 mL). The combined dichloromethane layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated to give 0.47 g of a yellow oil. The residue was dissolved in 25

2

2

concentrated. The residue was crystallized with ethyl acetate and hexane to

ຊ

mL of 25% ethyl acetate in hexane and filtered through silica and

WO 00/47568

PCT/US00/02503

308

give 301.6 mg of N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]benzenesulfonamide as a yellow solid.

Step 4. (4R,5R)-3,3-dibutyl-7-{dimethylamino}-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide and (46,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

To a solution of 150 mg (0.31 mmol) of the material prepared in Step 3 above in 6 mL of tetrahydrofuran cooled to -15 °C was added 0.90 mL 1 M of potassium t-butoxide in tetrahydrofuran. The reaction mixture was stirred for

2

15 minutes at -15 °C and then water was added. The organics were evaporated and 100 nL of ethyl acetate was added and then extracted. The ethyl acetate layer was washed with brine (100 nL), dried over magnesium sulfate and concentrated to form a residue. The residue was purified by flash chromatography with 30% ethyl acetate in hexane as eluent to give 61.8 mg of (4S,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide, and 65.7 mg of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide. <sup>1</sup>H NMR and mass spectra were consistent with the product.

12

- Example 14
- 20 (4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,2-benzothiazepin-4-ol 1,1-dioxide

309

The procedure of Example 2 above was followed except that (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide was used in place of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide. <sup>1</sup>H NMR was consistent with the product. MS (M\*) 460.

#### xample 15

5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl)phenyl]pentanamide

5

Z O T NH

WO 00/47568 PCT/US00/02503

310

The procedure of Example 3 above was followed except that (4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,2-benzothiazepin-4-ol 1,1-dioxide was used in place of (4R,5R)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide. <sup>1</sup>H NMR was consistent with the product. MS (M+H\*) 623.

#### Example 16

5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-1-

pentanaminium trifluoroacetate

5

To a solution of 54.1 mg (0.09 mmol) of the bromide prepared in Example 15 above in 1 mL of tetrahydrofuran was added 48 µL of triethylamine. The reaction mixture was heated at reflux for three days. The solvent was evaporated and the residue triturated with ether. The solid was purified by reverse phase high pressure liquid chromatography to give 17.9 mg of 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-y]]phenyl]amino]-N,N,N-triethyl-

11

5-oxo-1-pentanaminium trifluoroacetate as a white solid. <sup>1</sup>H NMR was consistent with the product. MS (M°) 643.

Example 17

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-phenyl-1,2-

benzothiazepin-4-ol 1,1-dioxide

Step 1-2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-(phenylmethyl)benzenesulfonamide

The procedure of Steps 1-2 of Example 7 was followed except that N-[1-butyl-1-[[[(1,1dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-

(dimethylamino)benzenesulfonamide and benzyl chloride were used in place of N-[1-butyl-1-[[[(1,1dimethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-N-methylbenzenesulfonamide and p-methoxybenzyl

WO 00/47568

PCT/US00/02503

312

chloride.

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-(phenylmethyl) benzenesulfonamide

The procedure of Step 3 of Example 13 was followed except that N-{1-

butyl-1-(ftydroxymethyl)pentyl]-4-(dimethylamino)-2-(phenylmethyl) benzenesulfonamide was used in place of N-[1-butyl-1-(hydroxymethyl) pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]benzenesulfonamide. Step 4. (4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-phenyl-1,2-benzothiazepin-4-ol 1,1-dioxide The procedure Step 4 of Example 7 was followed except that N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-(phenylmethyl)
benzenesulfonamide was used in place of N-[1-butyl-1-formylpentyl]-4
(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-methylbenzenesulfonamide. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8 0.9 (m, 6H), 1-1.7 (m, 13H), 2.3 (m, 1H),

15 2.8 (s, 6H), 4.0 (s, 2H), 5.5 (s, 1H), 5.9 (s, 1H), 6.5 (m, 1H), 7.4 (m, 3H), 7.5 (m, 2H), 7.8 (m, 1H). MS (M+H\*) 445.0.

PCT/US00/02503

313

Example 18

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

Step 1. N-[1-Butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[[4-methoxyphenyl)methyl]benzenesulfonamide

The procedure of Step 1 of Example 7 was followed except that N-[1-butyl-1-[[[(1,1dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4.

(dimethylamino)benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1,1dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-N-methylbenzenesulfonamide.

5

WO 00/47568 PCT/US00/01503

314

Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]benzenesulfonamide

The procedure of Step 8 of Example 1 was followed except that N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4[(dimethylamino)-2-[(4-methoxyphenyl)methyl]benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl] pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide.

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl) 10 methyl]benzenesulfonamide

PCT/US00/02503

315

The procedure of Step 3 of Example 13 was followed except that N-[1-butyl-1-(hydroxymethyl)pentyl].4-(dimethylamino)-2-[(4-methoxyphenyl) methyl]benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethyl]thyl]dimethylsilyl]oxy]methyl]pentyl].4-(dimethylamino)-2-[(3-nitophenyl)methyl]-N-methylbenzenesulfonamide.

Step 4. (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

The procedure of Step 10 of Example 1 was followed except that N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl] benzenesulfonamide was used in place of N-[1-butyl-1-formylpentyl]-4- (dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide. ¹H NMR (CDCI), 8 0.89-1.00 (m, 6H), 1.06-1.73 (m, 11H), 2.36 (t, J=9.5 Hz, 1H), 2.80 (s, 6H), 2.98 (s, 1H), 3.85 (s, 3H), 3.97 (s, 1H), 4.03 (d, J=9.0 Hz, 1H), 5.47 (s, 1H), 6.00 (d, J=2.4 Hz, 1H), 6.50 (dd, J=2.6, 8.9 Hz, 1H), 6.95 (d, J=8.8 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 7.81 (d, J=8.7 Hz, 1H).

2

#### Example 19

15

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

WO 00/47568

PCT/US00/02503

316

The procedure set forth in Example 8 above was followed except that (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-terahydro-5-(4-methoxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide was used in place of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-2-methyl-1,2-

benzothiazepin-4-ol 1,1-dioxide and a reaction temperature of 0 °C was employed. 'H NMR (CDCI<sub>3</sub>) 8 0.86-0.97 (m, 6H), 1.15-1.75 (m, 11H), 2.35 (t, J=9.9 Hz, 1H), 2.80 (s, 6H), 3.98 (s, 1H), 4.02 (d, J=8.6 Hz, 1H), 5.12 (s, 1H), 5.45 (s, 1H), 5.98 (d, J=2.4 Hz, 1H), 6.48 (dd, J=2.6, 8.6 Hz, 1H), 6.88 (d, J=8.8 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.80 (d, J=8.7 Hz, 1H).

### 10 · Example 20

2-[2-[2-[4-[(4R,SR)-3,3-dibutyl-7- (dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-y]phenoxy]ethoxy]ethoxy]-N,N,N-triethylethanaminium iodide

Step 1

317

The procedure set forth in Example 9 above was followed except that (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

- hydroxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide was used in place of (4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-(((2-iodoethyoxy)ethoxy)ethoxy)phenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide and 3.3 equivalents of 95% sodium hydride was used instead of 2.2 equivalents. <sup>1</sup>H NMR was consistent with the product.
- 10 Step 2. 2-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]-N,N,N-triethylethanaminium iodide

The procedure set forth in Example 10 above was followed except that the benzothiazepine prepared in Step 1 above was used. 'H NMR (CDCl<sub>3</sub>) & 0.88-0.05 (m, 6H), 1.14-1.60 (m, 20H), 2.31-2.39 (m, 1H), 2.82 (s, 6H), 3.06-

2

WO 00/47568 PCT/US00/02503

318

3.15 (m, 2H), 3.54 (q, *J* = 7.3 Hz, 6H), 3.75-3.81 (m, 4H), 3.88-4.17 (m, 7H), 5.47 (s, 1H), 5.98-6.02 (m, 1H), 6.47-6.54 (m, 1H), 6.93-6.98 (m, 2H), 7.42-7.47 (m, 2H), 7.81-7.84 (m, 1H).

#### xample 21

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

Step 1. N-[1-Butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-(phenylmethyl) benzenesulfonamide

PCT/US00/02503

91

To a solution of 4.24 g (7.0 mmol) of the sulfonamide prepared in Step 1 of Example 13 in 30 mL of acetone was added 2.90 g of potassium carbonate, 0.517 g of tetra-n-butylammonium iodide then 2.394 g of benzyl bromide. The reaction mixture was heated at reflux for five daya. To the reaction mixture was added 2.394 g of benzyl bromide, 0.517 g of tetra-n-butylammonium iodide, and then 2.90 g of powdered potassium carbonate. The reaction mixture was heated at reflux for one day. To the reaction mixture 250 mL of ethyl acetate was added. The ethyl acetate solution was washed with water (3 x 100 mL) and brine (200 mL). The ethyl acetate layer was

dried over magnesium sulfate and concentrated to a residue. The residue was purified by flash chromatography to give 1.82 g of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide.

Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide

The procedure of Step 8 of Example 1 was followed except that N-[1-butyl-1-[[((1-dimethyl)chtyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl]methyl]-N-(phenylmethyl) benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-

WO 00/47568

PCT/US00/02503

330

dimethylethyl)dimethylsilyl)oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide.

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide

The procedure of Step 3 of Example 13 was followed except that N-[1-Butyl-1-{hydroxymethyl}]-4-{dimethylamino}-2-{(3-nitrophenyl}) methyl]-N-{phenylmethyl})benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-{(dimethylamino}-2-{(3-nitrophenyl)methyl]benzenesulfonamide.

Step 4. (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide

The procedure of Step 10 of Example 1 was followed except that N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide was used in place of N-[1-butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide. <sup>1</sup>H NMR was consistent with the product. MS (M+H) 580.

13

321

Example 22

tetrahydro-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide (4R,SR)-3,3-dibutyl-7-(dimethylamino)-5-[3-(ethylamino)phenyl]-2,3,4,5-

2 4 of Example 21 in 50 mL ethanol was added about 10 mg of Pearlman's  $(CDC_{1})$   $\delta$  0.72 (t, J = 6.6, 3H), 0.90 (t, J = 7.4 Hz), 1.00-1.98 (m, 15H), 2.81 was dried over magnesium sulfate and concentrated to give 39.8 mg of a washed with water (2 x 50 mL) and brine (50 mL). The ethyl acetate layer Catalyst. This mixture was hydrogenated at 60 psi  $H_2$  for 20 hours. To the 6.83 (m, 1H), 6.95-7.00 (m, 1H), 7.16-7.31 (m, 5H), 7.40 (d, J = 7.2 Hz, 1H), (s, 6H), 3.17 (q, J = 7.2 Hz, 2H), 4.15 (d, J = 7.8 Hz, 1H), 4.39 (s, 2H), 5.69residue. The residue was purified by flash chromatography to give 12.6 mg of mixture was filtered and washed with 50 mL of ethyl acetate. The filtrate was mixture was hydrogenated at 60 psi at 60 °C for 20 hours. The reaction reaction mixture was added about 10 mg of Pearlman's Catalyst and the 7.81 (d, J = 8.7 Hz, 1H). MS (M+H\*) 578. (s, 1H), 6.12 (s, 1H), 6.47 (dd, J = 2.7, 9.0 Hz, 1H), 6.61-6.65 (m, 1H), 6.78tetrahydro-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide. 1H NIMR (4R,5R)-3,3-dibutyl-7-(dimethylamino)-5-[3-(ethylamino)phenyl]-2,3,4,5-To a solution of 50 mg (0.09 mmol) of the compound prepared in Step

5

WO 00/47568 PCT/US00/02503

322

methoxyphenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-

(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-(phenylmethyl)benzenesulfonamide Step 1. N-[1-Butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-

PCT/US00/02503

mg of 95% sodium hydride and then 964 µL of benzyl bromide. The reaction solution (100 mL) and brine (150 mL). The ethyl acetate layer was dried over mixture was stirred 18 hours. To the reaction mixture was added 250 mL of ethyl acetate and the mixture was washed with saturated sodium bicarbonate Step 1 of Example 7 above in 30 mL of dimethylfornamide was added 123 To a solution of 2.15 g (4.05 mmol) of the sulfonamide prepared in dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(4magnesium sulfate and concentrated to give 2.88 g of N-[1-butyl-1-[[[(1methoxyphenyl)methyl}-N-(phenylmethyl)benzenesulfonamide.

2

Step 2. N-[1-Butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(4methoxyphenyl)methyl]-N-(phenylmethyl)benzenesulfonamide

The procedure of Step 8 of Example 1 was followed except that N-[1. butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-

2

(phenylmethyl)benzenesulfonamide was used in place of N-[1-butyl-1-[[[(1dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3nitrophenyl)methyl]-N-methylbenzenesulfonamide.

Step 3. N-[1-Butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-

WO 00/47568

324

nitrophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide

The procedure of Step 3 of Example 13 was followed except that N-[1butyl-1-(hydroxymethyl)pentyl]-4-(dimethylamino)-2-[(4-

place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl].4methoxyphenyl)methyl]-N-(phenylmethyl)benzenesulfonamide was used in (dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide.

Step 4. (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4methoxyphenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide The procedure of Step 10 of Example 1 was followed except that N-[1methylbenzenesulfonamide. <sup>1</sup>H NMR (CDCI<sub>3</sub>) § 0.7 (m, 3H), 0.9 (m, 3H), 1butyl-1-formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-(phenylmethyl)benzenesulfonamide was used in place of N-[1-butyl-1formylpentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-2

1.7 (m, 10H), 1.9 (m, 1H), 2.1 (m, 1H), 2.8 (s, 6H), 3.8 (s, 3H), 4.1 (s, 1H), 4.4 (s, 2H), 5.8 (s, 1H), 6.0 (s, 1H), 6.5 (m, 1H), 7.0 (d, J=8 Hz, 1H), 7.1-7.5 (m, 7H), 7.8 (m, 1H). 12

325

spiro[1,2-benzothiazepine-3(2H),1'-cyclopentan]-4-ol 1,1-dioxide (4R,5R)-7-dimethylamino)-2-ethyl-4,5-dihydro-5-(4-methoxyphenyl)-

Step 1. N-[1-(hydroxymethyl)cyclopentyl]-4-fluorobenzenesulfonamide

cycloleucinol was substituted for 2-amino-2-butylhexanol. The procedure of Step 2 of Example 1 was followed except that

(dimethylamino)benzenesulfonamide Step 2-3. N-[1-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]cyclopentyl]-4-

The procedure of Steps 3 and 4 of Example 1 was followed except that

WO 00/47568

PCT/US00/02503

326

place of N-[1-butyl-1-(hydroxymethyl)pentyl]-4-fluorobenzenesulfonamide.N-[1-(hydroxymethyl)cyclopentyl]-4-fluorobenzenesulfonamide was used in

(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-methylbenzenesulfonamide Step 4. N-[1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]cyclopentyl]-4-

methylbenzenesulfonamide.  $[[[(1,l\, dimethylethyl)dimethylsilyl]oxy] methyl]pentyl]-4-(dimethylamino)-N-lethyllogram and the state of   $[[[(1,1-{\rm dimethylethyl}){\rm dimethylsilyl}] oxy] methyl] cyclopentyl]-4-$ (dimethylamino)benzenesulfonamide was used in place of N-[1-butyl-1-The procedure of Step 1 of Example 7 was followed except that N-[1-

10

methoxyphenyl) methyl] - N-ethylbenzenesul fon a mideStep 5. N-[1-(hydroxymethyl)cyclopentyl]-4-(dimethylamino)-2-[(4-

68 PCT/US00/02503

327

To a solution of 0.25 g (0.49 mmol) of the sulfonamide prepared in Step 4 above in 5 mL of tetrahydrofuran was added 25 mg of 95% sodium hydride. After 15 minutes, 125 µL of ethyl iodide was added to the reaction mixture was stirred 16 hours. To the reaction mixture was added 5 mL of dimethylformamide and the mixture stirred four hours. To the reaction mixture was added 5 mL of dimethylformamide and the mixture stirred four hours. To the reaction mixture 100 mL of water was added and the mixture extracted with 100 mL of ethyl acetate. The ethyl acetate layer was washed with brine (100 mL), dried over magnesium sulfate and concentrated to give 0.27g of an oil.

10 Step 6-8. (4R,5R)-7-dimethylamino)-2-ethyl-4,5-dihydro-5-(4-methoxyphenyl)-spiro[1,2-benzothiazepino-3(2H),1'-cyclopentan]-4-ol 1,1-dioxide

The procedure of Steps 8-10 of Example 1 was followed except that N-[1-(hydroxymethyl)cyclopentyl]-4-(dimethylamino)-2-[(4-methoxyphenyl)methyl]-N-ethylbenzenesulfonamide was used in place of N-[1-butyl-1-[[[(1-dimethylethyl)dimethylsilyl]oxy]methyl]pentyl]-4-(dimethylamino)-2-[(3-nitrophenyl)methyl]-N-methylbenzenesulfonamide. ¹H NMR was consistent with product. MS (M+H\*) 445.

13

### Biological Assays

2

The utility of the compounds of the present invention is shown by the following assays. These assays are performed in vitro and in animal models essentially using a procedure recognized to show the utility of the present invention.

In Vitro Assay Of Compounds That Inhibit IBAT-Mediated Uptake Of ["C]-

25 Taurocholate (TC) in H14 Cells

Baby hamster kidney cells (BHK) transfected with the cDNA of

WO 00/47568

PCT/US00/02503

human IBAT (H14 cells) are seeded at 60,000 cells/well in 96 well Top-Count tissue culture plates for assays run within 24 hours of seeding; 30,000 cells/well for assays run within 48 hours; and 10,000 cells/well for assays run within 72 hours.

- On the day of assay, the cell monolayer is gently washed once with 100 mL assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin ((FAF)BSA). To each well 50 mL of a two-fold concentrate of test compound in assay buffer is added along with 50 mL of 6 mM [<sup>14</sup>C]-taurocholate in assay buffer (final
- oconcentration of 3 mM [<sup>14</sup>C]-taurocholate). The cell culture plates are incubated two hours at 37° C prior to gently washing each well twice with 100 mL of 4° C Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed once with 100 mL of 4° C PBS without (FAF)BSA. To each 200 mL of liquid scintillation counting fluid is
  - 15 added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay Of Compounds That Inhibit Uptake Of I"CI-Alanine

The alanine uptake assay is performed in an identical fashion to the

20 taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate. Data from each of the noted compounds in this assay is as set forth in Table 4 below:

329

Table 4

	COMPOUND	HUMAN TC IC,	ALANINE UPTAKE
	(EXAMPLE	(μM)	IC,
	NUMBER)		
5	1	1.2	
	2	0.32	
	3	0.69	
	4	0.083	>100
	S	0.97	
0	6	0.32	
	7	0.57	
	8	0.58	
	10	0.31	
	11	0.20	
5	12	1.2	
	13 (cis)	0.044	
	13 (trans)	0.21	
	14	0.006	
	15	0.022	
õ	16	0.0016	
	17	0.035	
	18	0.026	
	19	0.003	>100
	20	0.008	
is	21		>1.0
	22	2.5	
	24	13.9	

WO 00/47568 PCT/US00/02503

330

# In Vivo Assay Of Compounds That Inhibit Rat Ileal Uptake Of [14C]-

Taurocholate into Bile

(See "Metabolism of 3α,7βdihydroxy-7β-methyl-5β-cholanoic acid and 3α,7β-dihydroxy-7α-methyl-5β-cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum), 20 mL of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 minutes with warm PBS at 0.25 mL/minute. Temperature of the gut segment is monitored continuously. At the start of the experiment, 2.0 mL of control sample (1"C]-taurocholate @ 0.05 mi/mL with 5 mM cold taurocholate) is loaded into the gut segment with a 3 mL syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 mL/minute for 21 minutes. Bile samples fractions are collected every three

5

5

25 but with the test compound being administered as well (21 minutes administration followed by 21 minutes of wash out) and bile sampled every three minutes for the first 27 minutes. If necessary, a third perfusion is performed as above that typically contains the control sample.

minutes for the first 27 minutes of the procedure. After the 21 minutes of sample infusion, the iteal loop is washed out with 20 mL of warm PBS (using a 30 mL syringe), and then the loop is washed out for 21 minutes with warm PBS at 0.25 mL/minute. A second perfusion is initiated as described above

20

331

Measurement Of Hepatic Cholesterol Concentration (HEPATIC CHOL.)

Liver tissue is weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant is separated and dried under nitrogen. The residue is dissolved in isopropanol and the cholesterol

content is measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) Clin. Chem. 20,

470

## Measurement Of Hepatic HMG CoA-Reductase Activity (HMG COA)

Hepatic microsomes are prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material is resuspended in buffer and an aliquot is assayed for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of <sup>14</sup>C-HMG-CoA (Dupont-NEN). The reaction is stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant is separated, by thin-

2

15 layer chromatography, and the spot corresponding to the enzyme product is scraped off the plate, extracted and radioactivity is determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) J. Lipid Res. 31, 2150)

Determination Of Serum Cholesterol (SER, CHOL, HDL-CHOL, TGI and

20 VLDL+LDL

Total serum cholesterol (SER.CHOL) is measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) is assayed using this same kit after precipitation of VLDL and LDL with Sigma

25 Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dexuran sulfate method). Total serum triglycerides (blanked) (TGI) are assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL

WO 00/47568

PCT/US00/02503

332

(VLDL + LDL) cholesterol concentrations are calculated as the difference between total and HDL cholesterol.

Measurement Of Henatic Cholesterol 7-a Hydroxylase Activity (7a-OHase)

Hepatic microsomes are prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material is resuspended in buffer and an aliquot is assayed for cholesterol 7-a-hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent is evaporated and the residue is dissolved in acetonitrile/ methanol. The enzymatic product is separated by injecting an aliquot of the extract onto a C<sub>11</sub> reversed phase HPLC column and quantitating the eluted material using UV detection at 240mm. (Reference: Horton, 1. D., et al. (1994)

Rat Gayage Assay

J. Clin. Invest. 93, 2084).

Male Wister rats (275-300g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:00 a.m.) for four days at varying dosages in a final volume of 2 mL per kilogram of body weight. Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for

bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group. Table 5 describes the results of this assay when the compound of Example 4 was tested.

333

Table 5

COMPOUND	DOSE (mg/kg/day)	% INCREASE IN
(EXAMPLE		FECAL BILE ACID
 NUMBER)		CONCENTRATION
4	5	217.2
4	0.4	157.8
4	0.04	244.0

## Measurement Of Fecal Bile Acid Concentration (FBA)

5

Total fecal output from individually housed hamsters is collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram is weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue is dissolved in methanol and the amount of bile acid present is measured enzymatically using the 3α-hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., et al. (1981) Clin. Chem. 27, 1352).

2

# (PHitaurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMY) Rabbit IIeal brush border membranes are prepared from frozen ileal

mucosa by the calcium precipitation method described by Malathi et al.

(Reference: (1979) Biochimica Biophysica Acta, 554, 259). The method for measuring taurocholate is essentially as described by Kramer et al. (Reference: (1992) Biochimica Biophysica Acta, 1111, 93) except the assay volume is 200 µL instead of 100 µL. Briefly, at room temperature a 190 µL solution

20

containing 2μM [<sup>2</sup>H]-taurocholate(0.75 μCi), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 is incubated for 5 seconds with 10 μL of brush border membrane vesicles (60-120 μg protein). The incubation is initiated by the addition of the BBMV while vortexing and the reaction is stopped by the

WO 00/47568

PCT/US00/02503

334

addition of 5 mL of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 μm pore) and an additional 5 mL wash with stop buffer.

## Acyl-CoA: cholesterol Acyl Transferase (ACAT)

20 2 ಠ with similar success by substituting the generically or specifically described preceding examples TLC plate with a Packard instaimager. The examples herein can be repeated The amount of cholesterol ester formed is determined by measuring the thorough vortexing. The chloroform phase is taken to dryness and then and aqueous phases of the extraction are separated by centrifugation after cholesterol oleate in chloroform methanol to act as a carrier and the organic of chloroform/methanol (2:1). To the extraction is added 125 µg of protein. The assay is initiated by the addition of oleoyl-CoA. The reaction reactants and/or operating conditions of this invention for those used in the amount of radioactivity incorporated into the cholesterol oleate spot on the spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). proceeds for five minutes at 37° C and is terminated by the addition of 8.0 mL mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 µg of microsomal containing 24 µM Oleoyl-CoA (0.05 µCi) in a 50 mM sodium phosphate, 2 a source of ACAT enzyme. The assay consists of a 2.0 mL incubation described previously (Reference: (1980) J. Biol. Chem. 255, 9098) and used as Hamster liver and rat intestinal microsomes are prepared from tissue as

The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

PCT/US00/02503

335

tin alaimed in

A compound of formula (I):

wherein:

2

q is an integer from 1 to 4;

15 R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen; hydrocarbyl; -OR<sup>2</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>2</sup>; -SO<sub>2</sub>R<sup>2</sup>; and -SO<sub>3</sub>R<sup>2</sup>; or

 $\rm R^3$  and  $\rm R^4$  together form =0; =NOR  $^9$  ; =S; =NNR  $^9\rm R^{10}$  ; =NR  $^9$  , or =CR  $^{11}\rm R^{12}$  ;

23

wherein R<sup>9</sup> and R<sup>10</sup> are independently selected from the group
consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino; wherein
said hydrocarbyl moeities may be optionally substituted with one or more
groups comprising one or more heteroatoms, and wherein said hydrocarbyl
moieties optionally may have one or more carbon atoms replaced by one or
more heteroatoms independently selected from the group consisting of
oxygen, nitrogen, sulfur and phosphorus; and

WO 00/47568

PCT/US00/02503

226

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; hydrocarbyl; -OR<sup>2</sup>; -NR<sup>2</sup>R<sup>10</sup>; -SR<sup>2</sup>; -S(O)R<sup>2</sup>; -SO2R<sup>9</sup>; and -SO3R<sup>9</sup>; wherein said hydrocarbyl moeities may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl moieties optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

33

 $\ensuremath{\mathbb{R}}^{11}$  and  $\ensuremath{\mathbb{R}}^{12}$  together with the carbon atom to which they are attached form a cyclic ring, and

6

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR<sup>2</sup>; -S(O)R<sup>2</sup>; -SO<sub>2</sub>R<sup>2</sup>; and -SO<sub>3</sub>R<sup>2</sup>;

\$

wherein the R<sup>5</sup> and R<sup>6</sup> radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen;

-NO<sub>2</sub>: -CN; oxo, hydrocarbyt; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; -SR <sup>13</sup>; -SO<sub>2</sub>R <sup>13</sup>; -NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -CO<sub>2</sub>R <sup>13</sup>; -OM; -SO<sub>2</sub>OMR <sup>13</sup>R <sup>14</sup>; -COONR <sup>13</sup>R <sup>14</sup>; -COORR <sup>13</sup>R <sup>14</sup>R <sup>14</sup>; -COORR <sup>13</sup>R <sup>14</sup>R <sup>14</sup>; -COORR <sup>13</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>R

SO\_ZOM; -SO\_ZNR <sup>13</sup>R <sup>14</sup>; -C(O)NR <sup>13</sup>R <sup>14</sup>; -C(O)OM; -COR <sup>13</sup>; .

NR <sup>13</sup>C(O)R <sup>14</sup>; -NR <sup>13</sup>C(O)NR <sup>18</sup>R <sup>15</sup>; -NR <sup>13</sup>CO,R <sup>14</sup>; -OC(O)R <sup>15</sup>; -OC(O)NR <sup>18</sup>R <sup>14</sup>; -NR <sup>13</sup>SO,R <sup>14</sup>; -NR <sup>13</sup>SO,R <sup>14</sup>; -NR <sup>13</sup>SO,NR <sup>18</sup>R <sup>13</sup>; -PR <sup>13</sup>R <sup>14</sup>A <sup>1</sup>; and -NC(O)R <sup>13</sup>R <sup>14</sup>A <sup>14</sup>A <sup>13</sup>R <sup>14</sup>A <sup>14</sup>A <sup>14</sup>A <sup>13</sup>R <sup>14</sup>A <sup>1</sup>

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>13</sup> are independently selected from the group consisting of hydrogen or hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; or

65 wherein R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally

337

substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

8

wherein A is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation; and

wherein R9 is as defined above; or

R4 and R6 together represent a bond; and

3

R<sup>N</sup> is selected from the group consisting of hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

8

one or more R<sup>x</sup> radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO2; hydrocarbyl; -OR13; -NR13<sub>R</sub>14; -SR13; -S(O)R13; -S(O)<sub>Z</sub>R13; -SO<sub>3</sub>R13; -S<sup>+</sup>R13<sub>R</sub>14<sub>K</sub>; -NR13<sub>OR14</sub>; -NR<sup>13</sup>OR14; -NR<sup>13</sup>OR14; -CO<sub>2</sub>R13; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>ORR<sup>13</sup>R14; -NR<sup>14</sup>C(O)R<sup>13</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR13; -S(O)<sub>M</sub>NR<sup>13</sup>R<sup>14</sup>; -N<sup>+</sup>R13<sub>R</sub>14<sub>R</sub>15<sub>A</sub>; -PR13<sub>R</sub>14; -P(O)R13<sub>R</sub>14; -P<sup>+</sup>R13<sub>R</sub>14<sub>R</sub>15<sub>A</sub>; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue, wherein said hydrocarbyl may be optionally substituted with one or more

8

groups comprising one or more heterostoms, and wherein said hydrocarby, optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; and

8

wherein n is 0, 1 or 2; and

wherein R13, R14, R15, A7, and M are as defined above; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof; and provided that at least one of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is a radical other than hydrogen or alkyl; and

છ

provided that when  $R^5$  or  $R^6$  is aryl, the other of  $R^5$  and  $R^6$  is a radical other than heterocycylalkyl.

100

WO 00/47568

PCT/US00/02503

<u>.</u>

2. A compound of claim I wherein:

q is an integer from 1 to 4;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclyl; alkoxyalkenyl; alkoxyalkynyl;

arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocylcyloxyalkyl; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl; or

R<sup>1</sup> and R<sup>2</sup> taken together with the carbon to which they are attached form C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl;

5

wherein the R<sup>1</sup> and R<sup>2</sup> alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkynyl; aryloxyalkynyl; aryloxyalkenyl; aryloxyalkynyl; heterocyclyloxyalkyl; heterocyclyloxyalkynyl;

alkylaryl; and (polyalkyl)aryl radicals optionally may be substituted with one or more radicals selected from the group consisting of -CN; halogen; oxo; -OR<sup>2</sup>; -NR<sup>2</sup>R<sup>10</sup>; -N<sup>+</sup>R<sup>2</sup>R<sup>10</sup>R<sup>W</sup>A<sup>-</sup>; -SR<sup>2</sup>; -SR<sup>2</sup>; -SR<sup>2</sup>R<sup>10</sup>A<sup>-</sup>; -PR<sup>2</sup>R<sup>10</sup>; -PR<sup>2</sup>R<sup>10</sup>; and P<sup>+</sup>R<sup>2</sup>R<sup>10</sup>R<sup>3</sup>WA<sup>-</sup>; -SO<sub>2</sub>R<sup>2</sup>; -SO<sub>2</sub>R<sup>2</sup>; -CO<sub>2</sub>R<sup>2</sup>; and -CONR<sup>2</sup>R<sup>10</sup>; and wherein the R<sup>1</sup> and R<sup>2</sup> alkyl; cycloalkyl; alkenyl; cycloalkenyl;

20 alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkyl; alkoxyalkynyl; aryloxyalkenyl; aryloxyalkynyl; heterocyclyloxyalkynyl; heterocycloxyalkenyl; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may have one or more carbons replaced by -O-; -NR<sup>9</sup>-; -N<sup>+</sup>R <sup>9</sup>R <sup>10</sup>A<sup>-</sup>; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R <sup>9</sup>A<sup>-</sup>-; -PR <sup>9</sup>-; -P(O)R <sup>9</sup>-; -P<sup>+</sup>R <sup>9</sup>R <sup>10</sup>A<sup>-</sup>-; or phenylene; and

wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>w</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and

wherein A is a pharmaceutically acceptable anion; and R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; or

carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR<sup>9</sup>; -NR<sup>9</sup>R <sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; wherein  $\mathrm{R}^{11}$  and  $\mathrm{R}^{12}$  are independently selected from the group heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; and -CONR 9R 10; or

<del>수</del>

 $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  together with the carbon atom to which they are attached form a cyclic ring; and

wherein R9 and R10 are as defined above; and

45

hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary  $R^5$  and  $R^6$  are independently selected from the group consisting of heterocyclyl; -OR<sup>9</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>;

wherein the  $R^5$  and  $R^6$  alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radicals optionally may be

substituted with one or more radicals independently selected from the group hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>; -NR<sup>13</sup>; -SR<sup>13</sup>; -SOOR<sup>13</sup>; -SO2R<sup>13</sup>; -SO3R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; CO2R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)OM;  $\cos^{13}$ ; -NR $^{12}$ COR $^{14}$ ; -NR $^{15}$ CO)NR $^{14}$ R $^{15}$ ; -NR $^{15}$ CO,R $^{14}$ ; -OC(O)R $^{13}$ ; consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; NR13SO,NR14R13, -PR13R14, -P(O)R13R14, -P+R13R14R15A; OC(0)NR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>SOR<sup>14</sup>; -NR<sup>13</sup>SO,R<sup>14</sup>; -P(OR 13)OR 14, -S+R 13R 14A; and -N+R 13R 14R 15A; and S 55 8

optionally may be further substituted with one or more radicals selected from heterocyclyt;  $-OR_{J_1}^{J_2}$ ,  $-NR_{J_1}^{J}R_{S_1}^{J_2}$ ,  $-S_1(Q)R_{J_2}^{J_2}$ ,  $-S_2(Q)R_{J_2}^{J_2}$ ;  $-S_2(Q)R_{J_2}^{J_2}$ ,  $-S_2(Q)R_{J_2}^{J_2}$ alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, CONR7RS; -NTR7R8R9A; -P(O)R7R8; -PR7R8; -PTR7R8R9A; and the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl, aikynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R3 and R6 radicals 2(O)(OR 1)OR 5; and

65

WO 00/47568

PCT/US00/02503

optionally may have one or more carbons replaced by -O.; -NR 7.; -N R R A. -: -S-; -SO-; -SO2-; -S<sup>+</sup>R<sup>7</sup>A-; -P(O)R<sup>7</sup>-; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-; or phenylene; wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R3 and R6 radicals 2 23

consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein R<sup>7</sup> and R<sup>8</sup> are independently selected from the group

뗥

wherein  $\mathbb{R}^{13}, \mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl;

8

heterocyclylalkyi; quaternary heterocyclylalkyl; alkylarylalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or aminocarbonylalkyl; alkylaminocarbonylalkyl;

wherein R13 and R14 together with the nitrogen atom to which they substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally oxo, carboxy, and quaternary salts; or 8

wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

wherein the R13, R14, and R15 alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quatemary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; 8

halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary aminocarbonylalkyl; alkylaminocarbonylalkyl; જ

N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>w</sup>A; -SR<sup>16</sup>, -S(O)R<sup>9</sup>, -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>, -CO<sub>2</sub>R<sup>16</sup>. CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; -P<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>11</sup>A. heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR16; -NR9R10; . S<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; and carbohydrate residue; and 8

S alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl;

= one or more carbons replaced by -O-; -NR2-; -NTR2 R10A-; -S-; -SO-; -SO2-;  $-s^+R^9A^-$ ;  $-PR^9$ -;  $-P^+R^9R^{10}A^-$ ;  $-P(O)R^9$ -; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

consisting of R and M; and

wherein M is a pharmaceutically acceptable cation; and

115

alkynyl; aralkyl; and heterocyclylalkyl; and RN is selected from the group consisting of hydrogen; alkyl; alkenyl; wherein R9, R10, R11, R12, Rw, and A are as defined above; and

120 heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy; -OR <sup>13</sup>; . NR <sup>13</sup>R <sup>14</sup>, -SR <sup>13</sup>, -S(O)R <sup>13</sup>; -S(O)2R <sup>13</sup>; -SO<sub>2</sub>R <sup>13</sup>; -S<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A; . NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -CO<sub>2</sub>R <sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR <sup>13</sup>R <sup>14</sup>; - NR <sup>13</sup>R <sup>14</sup>R <sup>14</sup>; - NR <sup>13</sup>R <sup>14</sup>R <sup>1</sup> consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary one or more RX radicals are independently selected from the group

125 P(O)R 13R 14; -P+R 13R 14R 15A; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

135 130 S<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; and carbohydrate residue; and CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PO(OR')OR', -P<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A; radicals selected from the group consisting of halogen; -CN; oxo; -OR 16, acyloxy radicals optionally may be further substituted with one or more alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; NR9R10; -N+R9R10RWA; -SR16; -S(O)R9; -SO2R9; -SO3R16; -CO2R16; wherein the R\* alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl

substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; wherein the R\* quaternary heterocyclyl radical optionally may be

> 45 SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, -C(O)NR<sup>13</sup>R<sup>14</sup>, -C(O)OM; -COR<sup>13</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>, -P<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -P(OR<sup>13</sup>)OR<sup>14</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>; heterocyclylalkyl; polyether; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; -SR <sup>13</sup>; -S(O)R <sup>13</sup>; -SO<sub>2</sub>R <sup>13</sup>; -SO<sub>3</sub>R <sup>13</sup>; -NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -CO<sub>2</sub>R <sup>13</sup>; OM; -SO<sub>2</sub>OM; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl;

N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; and carbohydrate residue; and

150 145 S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>.; -PR<sup>13</sup>-; -P(O)R<sup>13</sup>-; -PR<sup>13</sup>R<sup>14</sup>, -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>.; phenylene; amino residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally wherein the R<sup>x</sup> radicals comprising carbon optionally may have one or more carbons replaced by -O-; -NR  $^{13}$ ; -N<sup>+</sup>R  $^{13}$ R  $^{14}$ A-; -S-; -SO-; -SO<sub>2</sub>; -SO-; -SO2-; -S<sup>†</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-; or -P(O)R<sup>9</sup>-; and may have one or more carbons replaced by -O-; -NR 2; -N R R 10 A -; -S-; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide acid residue; peptide residue; polypeptide residue; carbohydrate residue; wherein  $\mathbb{R}^{18}$  is selected from the group consisting of alkyl; alkenyl;

155 heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;

heterocyclylalkoxycarbonyl; and wherein the R11 alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary

50 be substituted with one or more radicals selected from the group consisting of halogen; -CN; NO;; oxo; -OR9; -NR9R10; -N+R9R11R12A; -SR9; -S(O)R<sup>9</sup>;-SO<sub>2</sub>R<sup>9</sup>;-SO<sub>3</sub>R<sup>9</sup>;-CO<sub>2</sub>R<sup>9</sup>;-CONR<sup>9</sup>R<sup>10</sup>;-SO<sub>2</sub>OM;-SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>;-P(OR<sup>13</sup>)OR<sup>14</sup>;-PO(OR<sup>16</sup>)OR<sup>17</sup>; and -C(O)OM; and arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl;

defined above; or wherein R, A, and M are as

ន

a pharmaceutically acceptable salt, solvate, or prodrug thereof

A compound of claim 1 wherein

q is an integer from 1 to 4;

hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl;  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of

alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl; or

PCT/US00/02503

343

 $R^{1}$  and  $R^{2}$  taken together with the carbon to which they are attached form C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl;

radicals optionally may be substituted with one or more radicals selected from the group consisting of -CN; halogen; oxo; -OR9; -NR9R10; -N+R9R10RWAwherein the  $\mathbb{R}^1$  and  $\mathbb{R}^2$  alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; .SR<sup>9</sup>; -S'R'R"A; -PR<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R"A"; -S(0)R<sup>9</sup>; -S0<sub>2</sub>R<sup>9</sup>; -S0<sub>3</sub>R<sup>9</sup>; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl CO2R9; and -CONR9R10; and

2

wherein the R and R alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A--, -S: -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A--, -PR<sup>9</sup>-; -P(O)R<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A--, alkoxyalkyi; alkoxyalkenyi; alkoxyalkynyl; alkylaryi; and (polyalkyi)aryi radicals optionally may have one or more carbons replaced by -O-; -NR? or phenylene; and 2

consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; wherein R9, R10, and RW are independently selected from the group carboalkoxyalkyl; carboxyheterocyclyl; carboxyalkylamino; and acyl; and alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; wherein A is a pharmaceutically acceptable anion; and

2

hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR9; -NR9R10; -SR9;  $\mathbb{R}^3$  and  $\mathbb{R}^4$  are independently selected from the group consisting of S(O)R9; -SO2R9; and -SO3R9; or 22

R3 and R4 together form =0; =NOR9; =S; =NNR9R10; =NR9; or -CR11R12;

heterocyclyl; arylalkyl; carboxyalkyl; carboalkoxyalkyl; cycloalkyl; cyanalkyl; -OR9, -NR9R10, -SR9; -S(O)R9; -SO2R9; -SO3R9; -CO2R9; consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; wherein  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  are independently selected from the group and -CONR9R10; or ဓ

 $R^{1\, 1}$  and  $R^{1\, 2}$  together with the carbon atom to which they are attached form a cyclic ring; and 33

wherein R9 and R10 are as defined above; and

hydrogen; nlkyi; cycloalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary  $R^5$  and  $R^6$  are independently selected from the group consisting of heterocyclyl;  $-OR^9$ ;  $-SR^9$ ;  $-S(O)R^9$ ;  $-SO_2R^9$ ; and  $-SO_3R^9$ ;

WO 00/47568

PCT/US00/02503

substituted with one or more radicals independently selected from the group wherein the R<sup>5</sup> and R<sup>6</sup> alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radicals optionally may be consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; **\$** 

cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether,  $-\mathrm{OR}^{13}$ ;  $-\mathrm{NR}^{13}\mathrm{R}^{14}$ ;  $-\mathrm{SR}^{13}$ ;  $-\mathrm{S}(\mathrm{O})\mathrm{R}^{13}$ ;  $-\mathrm{SO}_2\mathrm{R}^{13}$ ;  $-\mathrm{SO}_3\mathrm{R}^{13}$ ;  $-\mathrm{OR}^{13}$ ;  $-\mathrm{OR}^{1$ NR<sup>13</sup>C(0)R<sup>14</sup>; -NR<sup>13</sup>C(0)NR<sup>14</sup>R<sup>15</sup>; -NR<sup>13</sup>C0,R<sup>14</sup>; -OC(0)R<sup>13</sup>; -OC(0)NR<sup>13</sup>R<sup>14</sup> -nr"sor", -nr"so,r", -nr"sonr"r"; -nr"so,nr"r"; -pr<sup>13</sup>R<sup>14</sup>, p(o)r<sup>13</sup>R<sup>14</sup>, -p<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -p(or<sup>13</sup>)or<sup>14</sup>, -s<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>; and -SO2OM; -SO2NR<sup>13</sup>R<sup>14</sup>; -C(0)NR<sup>13</sup>R<sup>14</sup>; -C(0)OM; -COR<sup>13</sup>; -\$

N+R13R14R15A: and S

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl,

alkenyl; alkynyl; aryi; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyli; -ORŽ; -NRŽRŠ; -SRŽ; -S(Q)RŽ; -SQZRŽ; -SOZRŽ; -COZRŽ; optionally may be further substituted with one or more radicals selected from CONR7R8; -NTR7R89A-; -P(O)R7R8; -PR7R8; -PTR7R8PA; andhe group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; heterocyclylalkyl, and polyether substituents of the R3 and R6 radicals 2

P(O)(OR7)OR8; and 8

optionally may have one or more carbons replaced by -0.; -NR7; -N+R7R8A. -; -S-; -SO-; -SO2-; -S<sup>+</sup>R<sup>7</sup>A-; -PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-; or phenylene; wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R3 and R6 radicals

જ

wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group consisting of hydrogen and alkyl; and

wherein R13, R14, and R15 are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; neterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; carboxyalkylaminocarbonylalkyl; and polyether, or alkylheterocyclylalkyl; alkylammoniumalkyl; 2

25

substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally oxo, carboxy, and quaternary salts; or wherein R13 and R14 together with the nitrogen atom to which they

are attached form a cyclic ring; and wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they

8

heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl;

radicals optionally may be substituted with one or more radicals selected from alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether the group consisting of halogen; -CN; sulfo; oxo; alkyl; sulfoalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;

æ

S(0)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>11</sup>A; -S<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A; and carboxyalkyl; guanidinyl; -OR16; -NR9R10; -N+R9R10RWA; -SR16; carbohydrate residue; and

heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy;

alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl;

8

phenylene; carbohydrate residue; amino acid residue; peptide residue; or N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·-; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·-; -P(O)R<sup>9</sup>alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether alkylheterocyclylalkył; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; radicals optionally may have one or more carbons replaced by -O-; -NR2-; -

8

polypeptide residue; and

consisting of Ry and M; and wherein  $R^{16}$  and  $R^{17}$  are independently selected from the group

alkynyi; and aralkyl; and  $\mathbb{R}^{N}$  is selected from the group consisting of hydrogen; alkyl; alkenyl; wherein R, Rio, Rii, Riz, R, and A are as defined above; and wherein M is a pharmaceutically acceptable cation; and

20

consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl; polyalkyl one or more RX radicals are independently selected from the group

WO 00/47568

PCT/US00/02503

115 ᇹ N+R13R14R15A-; -PR13R14; -P(O)R13R14; -P+R13R14R15A-; amino acid C(O)OM; -COR<sup>13</sup>; -OR<sup>18</sup>; -S(O)nNR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>R<sup>18</sup>; -NR<sup>18</sup>OR<sup>14</sup>; -CO2R 13; -OM; -SO2OM; -SO2NR 13R 14; -NR 14C(O)R 13; -C(O)NR 13R 14, arylalkyl; polyether; acyloxy; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; S(O)R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup> haloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl;

residue; peptide acid residue; polypeptide acid residue; and carbohydrate acid

120 S<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A ; and carbohydrate residue; and CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; -PR<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A; radicals selected from the group consisting of halogen; -CN; oxo; -OR<sup>16</sup>; -NR<sup>9</sup>R<sup>10</sup>, -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A; -SR<sup>16</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; and acyloxy radicals optionally may be further substituted with one or more alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; wherein the R\* alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl;

130 125 SO2NR 13R 14; -C(O)NR 13R 14; -C(O)OM; -COR 13; -P(O)R 13R 14; heterocyclylalkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; OM; -SO<sub>2</sub>OM; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; and carbohydrate residue; and PR 13R 14; -P+R 13R 14R 15A; -P(OR 13)OR 14; -S+R 13R 14A; and hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; substituted with one or more radicals selected from the group consisting of wherein the R\* quaternary heterocyclyl radical optionally may be

40 135 N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A<sup>\*</sup>-; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>†</sup>R<sup>9</sup>A--; -PR<sup>9</sup>-; -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A--; or -P(O)R<sup>9</sup>wherein the R<sup>x</sup> radicals comprising carbon optionally may have one or more carbons replaced by -O-; -NR <sup>13</sup>-; -N<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A-; -S-; -SO-; -SO<sub>2</sub>: -S<sup>+</sup>R <sup>13</sup>A<sup>-</sup>; -PR <sup>13</sup>-; -P(O)R <sup>13</sup>-; -PR <sup>13</sup>-; -P<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A-; phenylene; amino optionally may have one or more carbons replaced by -O-; -NR -; phenylene; amino acid; peptide; polypeptide; carbohydrate; and polyalkyl acid; peptide; polypeptide; carbohydrate; polyether; or polyalkyl; wherein said

alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; wherein  $\mathbb{R}^{18}$  is selected from the group consisting of alkyl; alkenyl;

heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and 145

be substituted with one or more radicals selected from the group consisting of halogen; -CN; oxo; -OR?; -NR $^9R^{10}$ ; -N^{4}R $^9R^{11}R^{12}A$ ; -SR $^9$ ; -S(O)R $^9$ ; -SO<sub>2</sub>R $^9$ ; -SO<sub>2</sub>R $^9$ ; -CONR $^9R^{10}$ ; -SO<sub>2</sub>ON; -SO<sub>2</sub>NR $^9R^{10}$ ; -PR $^9R^{10}$ ; -P(OR $^{13}$ )OR $^{14}$ ; -PO(OR $^{16}$ )OR $^{17}$ ; and -C(O)OM; and wherein the R13 alky1; alkenyl; alkynyl; aryl; heterocyclyl; quaternary arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; 50

a pharmaceutically acceptable salt, solvate, or prodrug thereof defined above; or

155

wherein R, R10, R11, R13, R11, R14, R15, R16, R17, R", A, and M are as

4. A compound of claim 1 wherein:

q is an integer from 1 to 4;

aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>2</sub>-C<sub>10</sub>)alkenyl; hydrogen; (C1-C10)alkyl; (C3-C10)cycloalkyl; (C3-C10)alkenyl; (C3-C10)alkynyl; R and R taken together with the carbon to which they are attached R1 and R2 are independently selected from the group consisting of (C,-C,0)alkoxy(C,-C,0)alkynyl; (C,-C,0)alkylaryl; and (polyalkyl)aryl; or form (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl;

one or more radicals selected from the group consisting of -CN; halogen; oxo; C10, alkylaryl; and (polyalkyl) aryl radicals optionally may be substituted with C<sub>10</sub>)alkenyl; (C<sub>1</sub>-C<sub>10</sub>)alkynyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; wherein the R and R2 (C1-C10)alkyl; (C3-C10)cycloalkyl; (C3-(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>2</sub>-C<sub>10</sub>)alkynyl; (C<sub>1</sub>-2

-OR9; -NR9R10; -N\*R9R10R\*A\*; -SR9; -S\*R\*R10A; -PR9R10; -PR\*R10R\*A\*; -SOONR9; -SOO3R9; -SOO3R9  $C_{10}) alkenyl; (C_2 - C_{10}) alkynyl; \, aryl(C_1 - C_{10}) alkyl; \, (C_1 - C_{10}) alkoxy(C_1 - C_{10}) alkyl;$ wherein the R1 and R2 (C1-C10)alkyl; (C3-C10)cycloalkyl; (C3-(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>2</sub>-C<sub>10</sub>)alkynyl; (C<sub>1</sub>-13

C10, alkylaryl; and (polyalkyl) aryl radicals optionally may have one or more

carbons replaced by -O-; -NR9-; -N<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A-; -S.; -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A--;

ន

PR<sup>9</sup>; -P(O)R<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>--</sup>; or phenylene; and

WO 00/47568

PCT/US00/02503

wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>W</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>3</sub>-C<sub>10</sub>)alkenyl; (C,-C10)alkynyl; aryl; heterocyclyl; ammonium(C1-C10)alkyl; (C1-

C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxyheterocyclyl; carboxy(C1-C10)alkylamino; and acyl; and 23

hydrogen; (C,-C<sub>10</sub>)alkyi; (C<sub>7</sub>-C<sub>10</sub>)alkenyi; (C,-C<sub>10</sub>)alkynyi; aryi; heterocyclyi; OR?; -NR $^9$ R $^10$ , -SR $^9$ ; -S(O)R?; -SO2R $^9$ ; and -SO3R $^9$ ; or R3 and R4 are independently selected from the group consisting of wherein A is a pharmaceutically acceptable anion; and ಜ

R3 and R4 together form =0; =NOR9; =S; =NNR9R10; =NR9; or -CR<sup>11</sup>R<sup>12</sup>:

(C<sub>2</sub>-C<sub>10</sub>)alkynyl; aryl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl;  $\begin{array}{l} {\rm carbo(C_1-C_{i0})alkoxy(C_1-C_{i0})alkyl; \, (C_3-C_{i0})cycloalkyl; \, cyano(C_1-C_{i0})alkyl; \, \cdot \\ {\rm OR}^2; \, -{\rm NR}^2{\rm R}^{10}; -{\rm SR}^2; \, -{\rm S(O)R}^2; \, -{\rm SO_2R}^2; \, -{\rm SO_3R}^2; \, -{\rm CO_2R}^2; \, and \, - \\ \end{array}$ consisting of hydrogen; -CN; halogen; oxo; (C1-C10)alkyl; (C2-C10)alkenyl; wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group CONR R 10; or 33

R<sup>11</sup> and R<sup>12</sup> together with the carbon atom to which they are attached form a cyclic ring; and **4** 

wherein R9 and R10 are as defined above; and

hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; (C<sub>7</sub>-C<sub>10</sub>)alkenyl; (C<sub>7</sub>-C<sub>10</sub>)alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR9; -SR9; -S(O)R9; -SO2R9;  $R^5$  and  $R^6$  are independently selected from the group consisting of

\$

radicals optionally may be substituted with one or more radicals independently C10 alkenyl; (C2-C10) alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl wherein the R5 and R6 (C1-C10)alkyl; (C3-C10)cycloalkyl; (C3and -SO3R9:

heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether,  $\cdot$ OR<sup>13</sup>;  $\cdot$ NR<sup>13</sup>R<sup>14</sup>;  $\cdot$ SO<sub>2</sub>R<sup>13</sup>;  $\cdot$ SO<sub>2</sub>R<sup>13</sup>;  $\cdot$ SO<sub>2</sub>R<sup>13</sup>;  $\cdot$ NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>;  $\cdot$ CO<sub>2</sub>R<sup>13</sup>;  $\cdot$ OM;  $\cdot$ (C<sub>2</sub>-C<sub>10</sub>)alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl C10, alkyi; polyalkyi; halo(C1-C10, alkyi; (C3-C10) cycloalkyi; (C2-C10, alkenyi; selected from the group consisting of halogen; -CN; -NO2; oxo; (C<sub>1</sub>-S

NR13C(0)R"; -NR13C(0)NR1'R13; -NR13C0,R"; -OC(0)R13; -OC(0)NR13R1;  ${
m SO_2OM; -SO_2NR^{13}R^{14}; -C(0)NR^{13}R^{14}; -C(0)OM; -COR^{13};}$ S

-NR<sup>15</sup>SOR"; -NR<sup>15</sup>O<sub>2</sub>R"; -NR<sup>15</sup>SONR''R<sup>1</sup>; -NR<sup>15</sup>SO,NR''R<sup>1</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -PR<sup>13</sup>R<sup>14</sup>, -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -P(OR<sup>13</sup>)OR<sup>14</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup> ; and -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; and

- S 8 (C2-C10)alkenyl; (C2-C10)alkynyl; aryl; heterocyclyl; aryl(C1-C10)alkyl; consisting of -CN; halogen; hydroxy; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; be further substituted with one or more radicals selected from the group C<sub>10</sub>)alkyl, and polyether substituents of the R<sup>3</sup> and R<sup>6</sup> radicals optionally may heterocyclyl, quaternary heterocyclyl, aryl(C1-C10)alkyl, heterocyclyl(C1- $C_{10}$ ) alkyl,  $(C_3-C_{10})$  cycloalkyl,  $(C_2-C_{10})$  alkenyl,  $(C_7-C_{10})$  alkynyl, aryl, wherein the (C<sub>1</sub>-C<sub>10</sub>)alkyl, polyalkyl, halo(C<sub>1</sub>-C<sub>10</sub>)alkyl, hydroxy(C<sub>1</sub>-
- 8  $P(O)R^7R^8$ ;  $-PR^7R^8$ ;  $-P^+R^7R^8R^9A^-$ ; and  $-P(O)(OR^7)OR^8$ ; and S(O)R'; -SO2R'; -SO3R'; -CO2R'; -CONR'R8; -N+R'R8R9A; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl; -OR'; -NR'R's; -SR'; -
- SO2-; -STR7A-; -PR7-; -P(O)R7-; -PTR7R8A-; or phenylene; and  $C_{10}$ )alkyl,  $(C_3$ - $C_{10}$ )cycloalkyl,  $(C_3$ - $C_{10}$ )alkenyl,  $(C_7$ - $C_{10}$ )alkynyl, aryl, have one or more carbons replaced by -O-; -NR '-; -NTR 'R'A-; -S-; -SO-; -C10) alkyl, and polyether substituents of the R' and R' radicals optionally may heterocyclyl, quaternary heterocyclyl, aryl(C1-C10)alkyl, heterocyclyl(C1wherein the (C<sub>1</sub>-C<sub>10</sub>)alkyl, polyalkyl, halo(C<sub>1</sub>-C<sub>10</sub>)alkyl, hydroxy(C<sub>1</sub>wherein  $R^{\overline{I}}$  and  $R^{\overline{B}}$  are independently selected from the group

z

consisting of hydrogen and (C1-C10)alkyl; and wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the group

carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether; or polyalkyl; (C2-C10)alkenyl; (C2-C10)alkynyl; aryl; heterocyclyl; quaternary C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary

8

oxo, carboxy, and quaternary salts; or substituted with one or more radicals selected from the group consisting of are attached form a mono- or polycyclic heterocyclyl that is optionally wherein R13 and R14 together with the nitrogen atom to which they

8

are attached form a cyclic ring; and wherein R 14 and R 15 together with the nitrogen atom to which they

ષ્ઠ

WO 00/47568

PCT/US00/02503

carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl (C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals  $C_{10}$ ) alky lheterocycly  $(C_1 - C_{10})$  alky  $(C_1 - C_{10})$  alky lammonium  $(C_1 - C_{10})$  alky  $(C_1$ C10)cycloalkyl; polyalkyl; (C2-C10)alkenyl; (C2-C10)alkynyl; aryl; heterocyclyl aminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-

95

8 C<sub>in</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>-C<sub>in</sub>)alkyl; guanidinyl; -OR<sup>16</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>-</sup>; -SR<sup>16</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; -CONR9R10; -- SO2NR9R10; -PO(OR16)OR17; -PR9R10; -P+R9R10R11A C10) alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl(C1group consisting of halogen; -CN; sulfo; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; sulfo(C<sub>1</sub>-

optionally may be substituted with one or more radicals selected from the

505 -S<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-; and carbohydrate residue; and wherein the R  $^{13},$  R  $^{14}$  , and R  $^{15}$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>-

115 <del>=</del>0 polypeptide residue; and NTRYR10A-;-S-;-SO-;-SO-;-STRYA-;-PRY-;-PTRYR10A-;-P(O)R9carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals aminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaminocarbonyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; phenylene; carbohydrate residue; amino acid residue; peptide residue; or optionally may have one or more carbons replaced by -O-; -NR9-; -C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyi(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylaryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl;  $C_{10}$ )cycloalkyl; polyalkyl;  $(C_2 - C_{10})$ alkenyl;  $(C_2 - C_{10})$ alkynyl; aryl; heterocyclyl;

consisting of Ry and M; and wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

RN is selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; wherein R, R, R, R, R, R, and A are as defined above; and wherein M is a pharmaceutically acceptable cation; and

(C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>2</sub>-C<sub>10</sub>)alkynyl; and aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; and

120

aryl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; C<sub>10</sub>)cycloalkyl; polyalkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>2</sub>-C<sub>10</sub>)alkenyl; (C<sub>2</sub>-C<sub>10</sub>)alkynyl; consisting of hydrogen; halogen; -CN; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>3</sub>one or more RX radicals are independently selected from the group

125

PCT/US00/02503

acyloxy; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -S(O)2R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -S<sup>1</sup>R<sup>14</sup>A<sup>2</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -NR<sup>13</sup>C(O)R<sup>13</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -OR<sup>13</sup>; -S(O<sub>II</sub>NR<sup>13</sup>R<sup>14</sup>; -NR<sup>18</sup>OR<sup>14</sup>; -NR<sup>18</sup>OR<sup>14</sup>; -NR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>2</sup>; -PR<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>, -P<sup>1</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>2</sup>; amino acid residue; peptide acid residue; polypeptide acid residue; and carbohydrate acid residue;

130

wherein the R¹ (C₁-C¹a)alkyl; (C₃-C¹a)cycloalkyl; polyalkyl; halo(C₁-C¹a)alkyl; hydroxy(C₁-C₁a)alkyl; (C₃-C₁a)alkenyl; (C₃-C₁a)alkynyi; aryl; heterocyclyl; aryl(C₁-C₁a)alkyl; heterocyclyl(C₁-C₁a)alkyl; polyether; and acylory anticals optionally may be further substituted with halogen; -CN; oxo; -OR¹6; -NRŶR¹0; -N+RŶR¹1R¹2A⁻; -SR¹6; -S(O)RŶ; -SO2RŶ; -SO3R¹6; -CO2R¹6; -CONRŶR¹0; -SO2NRŶR¹0; -PO(OR¹6)OR¹; -PRŶR¹1R²A⁻; or -S⁴RŶR¹0 Å; and

135

wherein the R' quaternary heterocyclyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO2; oxo; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)cycloalkyl; polyalkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; hydroxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkryl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; polyalkyl; aryl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyalkyl; hyll; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; hyll; hyll

wherein the R<sup>x</sup> radicals comprising carbon optionally may have one or more carbons replaced by -O.; -NR<sup>13</sup>; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A·; -S.·; -SO.; -SO.2.· S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>; -PR<sup>13</sup>, -P(O)R<sup>13</sup>; -PR<sup>13</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A·; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether, or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O.; -NR<sup>9</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·; -S.; SO.; -SO.2.; -S<sup>+</sup>R<sup>9</sup>A·; -PR<sup>9</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·; or -P(O)R<sup>9</sup>; and

wherein R<sup>18</sup> is selected from the group consisting of (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; acyl; and aryl(C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl; and

wherein the R<sup>11</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quatemary heterocyclyl; asyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; acyl; and aryl(C<sub>1</sub>-C<sub>10</sub>)alkoxycarbonyl radicals optionally

353

may be substituted with one or more radicals selected from the group consisting of halogen; -CN; oxo; -OR?; -NR $^9$ R. $^10$ ; -N $^4$ R $^3$ R. $^1$ R $^3$ R. $^2$ S(O)R $^9$ ; -SO2R $^9$ ; -SO2R $^9$ ; -CONR $^9$ R. $^10$ ; -SO2OM; -SO2NR $^9$ R. $^10$ ; -PR $^9$ R. $^1$ ; -P(OR $^1$ 3)OR $^1$ 4; -PO(OR $^1$ 6)OR $^1$ 7; and -C(O)OM; and

9

a pharmaceutically acceptable salt, solvate, or prodrug thereof; and provided that aryl is selected from the group consisting of optionally substituted phenyl, biphenyl and naphthyl; and

provided that heterocyclyl is selected from the group consisting of optionally substituted heterocyclyl comprising a 5 to 10 membered ring and comprising one or more ring atoms that are heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus.

5. A compound of claim 1 wherein:

q is an integer from 1 to 4;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tertbutyl, pentyl, hexyl, phenoxymethylene, phenoxyethylene, phenoxypropylene, pyridinyloxymethylene, pyridinyloxymethylene, pyridinyloxyethylene, pyrimidinyloxymethylene, methylpyridinyloxyethylene, pyrimidinyloxyethylene, or

S

 $R^1 \ {\rm and} \ R^2$  taken together with the carbon to which they are attached form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; and

2

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, phenyl, pyridinyl, amino, methylamino, dimethylamino, ethylamino and diethylamino; and

R<sup>2</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, hydroxyphenyl, methoxyphenyl, methoxyfchlorophenyl), methoxyfbromophenyl), methoxyfchlorophenyl), ethoxyfchlorophenyl), ethoxyfchlorophenyl), ethoxyfchlorophenyl), ethoxyfchlorophenyl), ethoxyfchlorophenyl, arminophenyl, methylaminophenyl, dimethylaminophenyl, dimethylaminophenyl, diethylaminophenyl,

trimethylammoniumphenyl, triethylammoniumphenyl,

z trimethylammoniumbutylcarbonylaminophenyl, triethylammoniumpropylcarbonylaminophenyl, triethylammoniumethylcarbonylaminophenyl, triethylammoniummethylcarbonylaminophenyl, trimethylammoniummethylcarbonylaminophenyl triethylammoniumbutylcarbonylaminophenyl, methylcarbonylaminophenyl trimethylammoniumpropylcarbonylaminophenyl, trimethylammoniumethylcarbonylaminophenyl,

ဗ္ဟ 엉 chloropropylcarbonylaminophenyl, fluoropropylcarbonylaminophenyl, ethylcarbonylaminophenyl, chloroethylcarbonylaminophenyl, chloromethylcarbonylaminophenyl, fluoromethylcarbonylaminophenyl, bromomethylcarbonylaminophenyl, iodomethylcarbonylaminophenyl, iodoethylcarbonylaminophenyl, propylcarbonylaminophenyl, fluoroethylcarbonylaminophenyl, bromoethylcarbonylaminophenyl,

8 ethoxycarbonylphenyl, trimethylammoniumethoxyethoxyethoxyphenyl methylpyridinyl, pyridinium, methylpyridinium, thienyl, chlorothienyl, triethylammoniumethoxyethoxyethoxyphenyl, butylcarbonylaminophenyl, chlorobutylcarbonylaminophenyl, bromopropylcarbonylaminophenyl, iodopropylcarbonylaminophenyl, fluorothicnyl, bromothicnyl, iodothicnyl; methoxycarbonylphenyl, iodobutylcarbonylaminophenyl, 3,4-dioxymethylenephenyl, pyridinyl, fluorobutylcarbonylarninophenyl, bromobutylcarbonylarninophenyl,

3 piperazinyloxymethoxyethoxyethoxyphenyl, pyridiniumethoxyethoxyethoxyphenyl, bromoethoxyethoxyethoxyphenyl, iodoethoxyethoxyethoxyphenyl chloroethoxyethoxyethoxyphenyl, fluoroethoxyethoxyethoxyphenyl,

methylpiperazinyloxymethoxyethoxyphenyl,

dimethylpiperidinyloxymethoxyethoxyethoxyphenyl; and methylpiperidinyloxymethoxyethoxyethoxyphenyl, and piperidinyloxymethoxyethoxyethoxyphenyl, dimethylpiperazinyloxymethoxyethoxyethoxyphenyl,

S

propyl, n-butyl, n-pentyl, n-hexyl and benzyl; and RN is selected from the group consisting of hydrogen, methyl, ethyl, n-

consisting of hydroxy, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl one or more Rx radicals are independently selected from the group

ટ

methylsulfinyl, methylsulfonyl, ethylthio, ethylsulfinyl, ethylsulfonyl, amino, hydroxyamino, methylamino, dimethylamino, ethylamino, diethylamino, tert-butyl, sec-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, methylthio,

8 trimethylammonium, triethylammonium, N-methyl-N-carboxymethyl-amino, bromomethylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino chloromethylcarbonylamino, fluoromethylcarbonylamino, N,N-dimethyl-N-carboxymethyl-ammonium, methylcarbonylamino,

2 pyrrolidine, N-methyl-pyrrolidinium, piperazinyl, N-methylpiperazinyl, N,N' hexylcarbonylamino, benzyloxycarbonylamino, aminoimidocarbonylamino, piperidinium, and thienyl; or dimethyl-piperazinium, piperidinyl, methylpiperidinyl, N-methylmorpholinyl, N-methyl-morpholinium, azetidinyl, N-methyl-azetidinium, n-propylcarbonylamino, n-butylcarbonylamino, n-pentylcarbonylamino, n-

a pharmaceutically acceptable sait, solvate, or prodrug thereof.

70

A compound of claim 1 wherein

q is an integer from 1 to 4;

hydrogen and (C<sub>1</sub>-C<sub>10</sub>)alkyl; or R1 and R2 are independently selected from the group consisting of

R1 and R2 taken together with the carbon to which they are attached

form (C3-C10)cycloalkyl; and  $\mathbb{R}^3$  and  $\mathbb{R}^4$  are independently selected from the group consisting of

hydrogen and hydroxy; and

5 more radicals independently selected from the group consisting of halogen;  $\label{eq:hydroxy; NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR <math display="inline">^{13}$ ; -NR  $^{13}R^{14}$ ; and -NR  $^{13}C(O)R^{14}$ ; R2 is phenyl, wherein said phenyl is optionally substituted with one or

2 consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether; or quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  are independently selected from the group

20 heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>wherein the R  $^{13}$ , R  $^{14}$ , and R  $^{15}$  (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl;

PCT/US00/02503 WO 00/47568

C10.)alkyl; quaternary heterocyclyl(C1-C10.)alkyl; (C1-C10.)alkylheterocyclyl(C1optionally may be substituted with one or more radicals selected from the C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals group consisting of halogen; (C1-C10) alkyl; heterocyclyl; quatemary

- consisting of hydrogen; (C1-C10)alkyl; heterocyclyl; ammonium(C1-C10)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>heterocyclyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>wherein R9 and R10 are independently selected from the group Clolalkyl; -OR16, -NR9R10, -NTR9R10RWA; and -CONR9R10; and 53
  - wherein R 11 and R 12 are independently selected from the group consisting of hydrogen; (C1-C10) alkyl; heterocyclyl; aryl(C1-C10) alkyl; C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxyheterocyclyl; carboxy(C1-C10)alkylamino; and acyl; and wherein A is a pharmaceutically acceptable anion; and ള
- R11 and R12 together with the carbon atom to which they are attached carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or form a cyclic ring; and 33

wherein R" and R16 are as defined in claim 2; and

R6 is hydrogen; and

RN is selected from the group consisting of hydrogen; (C1-C10) alkyl; one or more RX radicals are independently selected from the group consisting of hydrogen; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; -OR<sup>13</sup>; and aryl(C1-C10)alkyl; and NR 13R 14. <del>수</del>

a pharmaceutically acceptable salt, solvate, or prodrug thereof; and wherein R13 and R14 are as defined above; or

provided that aryl is selected from the group consisting of optionally substituted phenyl, biphenyl and naphthyl; and

optionally substituted heterocyclyl comprising a 5 to 10 membered ring and comprising one or more ring atoms that are heteroatoms selected from the provided that heterocyclyl is selected from the group consisting of group consisting of oxygen, nitrogen, sulfur and phosphorus. S

7. A compound of claim 1 wherein:

q is an integer from 1 to 4;

S

WO 00/47568

PCT/US00/02503

356

 $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of ethyl and n-butyl; or R and R taken together with the carbon to which they are attached form cyclopentyl; and one of R3 and R4 is hydrogen and the other of R3 and R4 is hydroxy; ဇွ

 $\mathbb{R}^5$  is selected from the group consisting of phenyl, hydroxyphenyl, methylaminophenyl, dimethylaminophenyl, ethylaminophenyl, methoxyphenyl, ethoxyphenyl, nitrophenyl, aminophenyl,

diethylaminophenyl, trimethylammoniumphenyl, triethylammoniumphenyl, rimethylammoniummethylcarbonylaminophenyl, triethylammoniummethylcarbonylaminophenyl, trimethylammoniumethylcarbonylaminophenyl, riethylammoniumethylcarbonylaminophenyl, 8

triethylammoniumbutylcarbonylaminophenyl, methylcarbonylaminophenyl, trimethylammoniumpropylcarbonylaminophenyl, rimethylammoniumbutylcarbonylaminophenyl triethylammoniumpropylcarbonylaminophenyl, 2

chioromethylcarbonylaminophenyl, fluoromethylcarbonylaminophenyl, bromomethylcarbonylaminophenyl, iodomethylcarbonylaminophenyl, chloropropylearbonylaminophenyl, fluoropropylearbonylaminophenyl fluoroethylcarbonylaminophenyl, bromoethylcarbonylaminophenyl, ethylcarbonylaminophenyl, chloroethylcarbonylaminophenyl, iodoethytcarbonylaminophenyl, propytcarbonylaminophenyl, 75

bromopropylcarbonylaminophenyl, iodopropylcarbonylaminophenyl, fluorobutylcarbonylaminophenyl, bromobutylcarbonylaminophenyl, butylcarbonylaminophenyl, chlorobutylcarbonylaminophenyl, iodobutylcarbonylaminophenyl, 8

trimethylammoniumethoxyethoxyethoxyphenyl,

83

bromoethoxyethoxyethoxyphenyl, iodoethoxyethoxyethoxyphenyl, and chloroethoxyethoxyphenyl, fluoroethoxyethoxyethoxyphenyl, triethylammoniumethoxyethoxyethoxyphenyl, pyridiniumethoxyethoxyethoxyphenyl; and

PCT/US00/02503

5

 $\mathbb{R}^N$  is selected from the group consisting of hydrogen, methyl, ethyl, and benzyl; and

8

one or more R<sup>X</sup> radicals are independently selected from the group consisting of hydroxy, methyl, ethyl, methoxy, ethoxy, amino, hydroxyamino, methylamino, dimethylamino, ethylamino, diethylamino,

છ

- trimethylammonium, triethylammonium, N-methyl-N-carboxymethyl-amino, N,N-dimethyl-N-carboxymethyl-ammonium, methylcarbonylamino, chloromethylcarbonylamino, fluoromethylcarbonylamino, bromomethylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino, benzyloxycarbonylamino, and aminoimidocarbonylamino; or.
- a pharmaceutically acceptable salt, solvate, or prodrug thereof.

**5** 

- A compound of claim 1 selected from the compounds of the group consisting of:
- (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;
- (4R,SR)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;
- 5-chloro-N-[3-[(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]pentanamide;

ಕ

- 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-pentanaminium trifluoroacetate;
- 2-chloro-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-y]]phenyl]acetamide;
- 2-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino]-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-2-oxoethanaminium chloride;

WO 00/47568

PCT/US00/02503

358

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-(((2-iodoethyoxy)ethoxy)ethoxy)phenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;

1-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethyl]pyridinium;

2-[2-[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-2-methyl-1,1-dioxido-1,2-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]-N,N,N-triethylethanaminium iodide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3methoxyphenyl)-2-methyl-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide and (4S,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,SR)-5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,2-benzothiazepin-4-ol 1,1-dioxide;

5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl)phenyl]pentanamide;

5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-1-pentanaminium trifluoroacetate;

(4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-phenyl-1,2benzothiazepin-4-ol 1,1-dioxide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4methoxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,SR)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;

2-[2-[2-[4-[(4R,5R)-3,3-dibutyl-7- (dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,2-benzothiazepin-5-y]phenoxy]ethoxy]ethoxy]-N,N,N-triethylethanaminium iodide;

(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide;

(4R,SR)-3,3-dibutyl-7-(dimethylamino)-5-[3-(ethylamino)phenyl]-2,3,4,5tetrahydro-2- (phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; (4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-2-(phenylmethyl)-1,2-benzothiazepin-4-ol 1,1-dioxide; and

(4R,SR)-7-dimethylamino)-2-ethyl-4,5-dihydro-5-(4-methoxyphenyl)-spiro[1,2-benzothiazepine-3(2H),1'-cyclopentan]-4-ol 1,1-dioxide; and

their pharmaceutically acceptable salts

9. A compound of claim 2 wherein  $R^5$  and  $R^6$  are independently selected from the group consisting of H; aryl; heterocyclyl; and quaternary heterocyclyl;

wherein the R<sup>5</sup> and R<sup>6</sup> ary!, heterocycly!, and quaternary heterocyclyl radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclyl; quaternary heterocyclyl; arylalkyl; holyether; -

S

WO 00/47568 PCT/US00/02503

360

OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; 
NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>1</sup>; -NR<sup>13</sup>CO)NR<sup>1</sup>; -NR<sup>13</sup>CO)NR<sup>1</sup>; -NR<sup>13</sup>CO)NR<sup>1</sup>; -NR<sup>13</sup>CONR<sup>1</sup>; -NR<sup>13</sup>CONR<sup>1</sup>; -NR<sup>13</sup>CONR<sup>14</sup>; -NR<sup>13</sup>CONR<sup>18</sup>; -NCO)R<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -P(A)R<sup>13</sup>R<sup>14</sup>; -P(A)R<sup>13</sup>R<sup>14</sup>; -P(A)R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>R<sup>14</sup>R<sup>13</sup>

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R³ and R⁴ radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl;

20 alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR<sup>7</sup>; -NR<sup>7</sup>R<sup>8</sup>; -S(O)R<sup>7</sup>; -S(O)R<sup>7</sup>; -SO2R<sup>7</sup>; -SO3R<sup>7</sup>; -CO3R<sup>7</sup>; -CONR<sup>7</sup>R<sup>8</sup>; -N<sup>4</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A; -P(O)R<sup>8</sup>; -P<sup>8</sup>R<sup>8</sup>; -P<sup>8</sup>R<sup>8</sup>R<sup>9</sup>A; and P(O)(OR<sup>7</sup>)OR<sup>8</sup>; and

wherein the alkyi, polyalkyi, haloalkyi, hydroxyalkyi, cycloalkyi, alkenyi, alkynyi, aryi, heterocyclyi, quaternary heterocyclyi, aryialkyi, heterocyclylalkyi, and polyether substituents of the R³ and R⁴ radicals optionally may have one or more carbons replaced by -O.; -NR<sup>7</sup>; -N<sup>+</sup>R, R³ A·; -S·; -SO; -SO2·; -S<sup>+</sup>R, A··; -PR, P; -P(O)R, P; -P<sup>+</sup>R, R³ A··; or phenylene;

wherein R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl;

alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;
heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl;
alkylheterocyclylalkyl; alkylarnmoniumalkyl; aminocarbonylalkyl;
alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or

wherein R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

各

wherein  $R^{14}$  and  $R^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

3

radicals optionally may be substituted with one or more radicals selected from alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quatemary heterocyclylalkyl; alkylarylalkyl;

S -OR<sup>16</sup>, NR<sup>9</sup>R<sup>10</sup>, N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>\*</sup>; -SR<sup>16</sup>, -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>, -CO<sub>2</sub>R<sup>16</sup>, -CONR<sup>9</sup>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, -PO(OR<sup>16</sup>)OR<sup>17</sup>, -PR<sup>9</sup>R<sup>10</sup>, -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>R<sup>11</sup>A<sup>\*</sup>; -S<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A<sup>\*</sup>; and carbohydrate residue; and the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary

alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl;

S

alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quaternary heterocyclytalkyl; alkylarylalkyl;

8

N<sup>†</sup>R<sup>†</sup>R<sup>†</sup>OA-; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>†</sup>R<sup>†</sup>A-; -PR<sup>†</sup>-; -P<sup>†</sup>R<sup>†</sup>R<sup>†</sup>OA-; -P(O)R<sup>9</sup>-; radicals optionally may have one or more carbons replaced by -O-; -NR9-; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether phenylene; carbohydrate residue; amino acid residue; peptide residue; or

consisting of R and M; and polypeptide residue; and wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group

ಬ

wherein R9, R10, R11, R12, Rw, and A are as defined in claim 2. wherein M is a pharmaceutically acceptable cation; and

5 A compound of claim 2 wherein R<sup>5</sup> or R<sup>6</sup> has the formula

-Ar-(R<sup>y</sup>),

G

t is an integer from 0 to 5;

piperazinyl; piperonyl; pyrrolyl; naphthyl; furanyl; anthracenyl; quinolinyl; isoquinolinyl; quinoxalinyl; imidazolyl; pyrazolyl; oxazolyl; isoxazolyl; Ar is selected from the group consisting of phenyl; thiophenyl; pyridyl;

WO 00/47568

PCT/US00/02503

5 pyrimidinyl; thiazolyl; triazolyl; isothiazolyl; indolyl; benzoimidazolyl; benzoxazolyl; benzothiazolyl; and benzoisothiazolyl; and one or more  $\mathbb{R}^{\mathbf{y}}$  are independently selected from the group consisting of

12 cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; -SR <sup>13</sup>; -SO<sub>3</sub>R <sup>13</sup>; -NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -CO<sub>2</sub>R <sup>13</sup>; -OM; -NR13C(0)R14; -NR13C(0)NR14R15; -NR13CO,R14; -OC(0)R13; -OC(0)NR13R14; SO2OM; -SO2NR 13R 14; -C(O)NR 13R 14; -C(O)OM; -COR 13; halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl;

20 -NR''SOR''; -NR''SO,R''; -NR''SONR''R'; -NR''SO,NR''R''; -P(O)R'13R'14, -PR'13R'14, -P+R'13R'14R'15A'; -P(OR'13)OR'14, -S+R'13R'14A'; and -N+R13R14R15A; and

8 ß aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR'; be further substituted with one or more radicals selected from the group N<sup>†</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A-; -P(O)R<sup>7</sup>R<sup>8</sup>; -PR<sup>7</sup>R<sup>8</sup>; -P<sup>†</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A<sup>\*</sup>; and -P(O)(OR<sup>7</sup>)OR<sup>8</sup>; -NR 7R 8; -SR 7; -S(O)R 7; -SO2R 7; -SO3R 7; -CO2R 7; -CONR 'R 5; consisting of -CN, halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclylalkyl, and polyether substituents of the RY radicals optionally may alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

SO2-; -S<sup>+</sup>R<sup>7</sup>A-; -PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-; or phenylene; and have one or more carbons replaced by O; -NR'; -N\*R'R'A.; -S.; -SO.; alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the RY radicals optionally may wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl,

ઝ

consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the group wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group

8 alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl;

7

wherein R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

45

wherein R  $^{14}$  and  $R\,^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

S

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; arylalkyl; heterocyclylalkyl; quatemary heterocyclylalkyl; alkylarylalkyl; alkylarylalkyl; alkylarmoniumalkyl; aminocarbonylalkyl; alkylarminocarbonylalkyl; alkylarminocarbonylalkyl; and polyether

radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR 16, -NR 9R 10, -N^R 9R 10R^A ~; -SR 16, -S(O)R 9; -SO2R 9; -SO3R 16; -SO2R 16, -SO3R 9R 10, -PO(OR 16) OR 17; -PR 9R 10; -PR 9R 10, -PR

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyi; haloalkyi; cycloalkyi; polyalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary heterocyclylalkyi; aryialkyi; heterocyclylalkyi; quaternary heterocyclylalkyi; alkylaryialkyi; alkylaryialkyi; alkylaryialkyi; alkylarminocarbonylalkyi; carboxyalkylarminocarbonylalkyi; carboxyalkylarminocarbonylalkyi; any have one or more carbons replaced by -O-; -NR\*; -

N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; -S.; -SO<sub>2</sub>; -S<sup>+</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; -P(O)R\*; phenylene; carbohydrate residue; amino acid residue; peptide residue; or 70 polypeptide residue; and wherein R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of R<sup>9</sup> and M; and

wherein M is a pharmaceutically acceptable cation; and wherein R, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>2</sup>, and A<sup>2</sup> are as defined in claim 2.

11. A compound of claim 2 wherein at least one of  $R^5$  and  $R^6\,\text{has}$  the formula

WO 00/47568

PCT/US00/02503

364

<del>}</del>

€

wherein R' and t are defined as in claim 10.

2

- 12. A compound of claim 11 wherein  $R^{\rm N}$  is selected from the group consisting of hydrogen, alkyl and aralkyl.
- A compound of claim 11 wherein R<sup>N</sup> is selected from the group consisting of bydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl and aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl.
- 14. A compound of claim 11 wherein  $\mathbb{R}^N$  is selected from the group consisting of hydrogen, methyl, ethyl and benzyl.
- A compound of claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, alkyl, and (C<sub>1</sub>-C<sub>10</sub>)cycloalkyl.
- 16. A compound of claim 11 wherein  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of hydrogen and (C,-C,0)alkyl.
- 17. A compound of claim 11 wherein  $\, {\rm R}^1$  and  ${\rm R}^2$  are independently selected from the group consisting of (C<sub>1</sub>-C<sub>10</sub>)alkyl.
- 18. A compound of claim 11 wherein  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of (C<sub>1</sub>-C<sub>2</sub>)alkyl.
- 19. A compound of claim 11 wherein  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of (C<sub>r</sub>-C<sub>s</sub>)alkyl.

PCT/US00/02503

365

- A compound of claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are the same (C<sub>1</sub>)alkyl.
- 21. A compound of claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting ethyl; n-propyl; n-butyl; and isobutyl.
- A compound of claim 11 wherein R<sup>1</sup> and R<sup>2</sup> are each n-butyl.
- 23. A compound of claim 11 wherein one of  $\mathbb{R}^1$  and  $\mathbb{R}^2$  is ethyl and the other of  $\mathbb{R}^1$  and  $\mathbb{R}^2$  is n-butyl.
- 4. A compound of claim 11 wherein q is 1, 2, or 3.
- 25. A compound of claim 11 wherein q is 1 or 2.
- 26. A compound of claim 11 wherein q is 1.
- 27. A compound of claim 11 wherein R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen and -OR<sup>9</sup>.
- 28. A compound of claim 27 wherein R<sup>9</sup> is hydrogen.
- A compound of claim 28 wherein said hydroxy group is in a syn relationship to said structure of formula (II).
- A compound of claim 11 wherein R<sup>x</sup> radicals are present at the
   8- and 9-positions of the benzo ring of the structure of formula (I).
- 31. A compound of claim 11 wherein an R<sup>X</sup> radical is present at one or more of the 7-, 8-, or 9-positions of the benzo ring of the structure of formula (I).
- A compound of claim 11 wherein R<sup>x</sup> radicals are present at the 7- and 9-positions of the benzo ring of the structure of formula (I).

PCT/US00/02503

ě

- A compound of claim 11 wherein an R<sup>X</sup> radical is present at the 7-position of the benzo ring of the structure of formula (I).
- 34. A compound of claim 32 wherein said one or more R<sup>X</sup> are independently selected from the group consisting of alkyl; aryl; cycloalkyl; heterocyclyl; polyalkyl; acyloxy; polyether; halogen; -OR <sup>13</sup>, -NR <sup>13</sup>R <sup>14</sup>, -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -N<sup>+</sup>R <sup>9</sup>R <sup>11</sup>R <sup>12</sup>A<sup>-</sup>; -SR <sup>13</sup>, -S<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A<sup>-</sup>; -CO<sub>2</sub>R <sup>13</sup>, and -NR <sup>14</sup>C(O)R <sup>13</sup>;

wherein alkyl; aryl; cycloalkyl; heterocyclyl; polyalkyl; acyloxy; and polyether; can be further substituted with -OR  $^{16}$ ; -NR  $^{9}R^{10}$ ; -N,  $^{4}R^{9}R^{10}R^{W}A^{-}$ ; -SR  $^{16}$ ; -S(O)R  $^{9}$ ; -SO2R  $^{9}$ ; -SO3R  $^{16}$ ; oxo; -CO2R  $^{16}$ ; -CN; halogen; -CONR  $^{9}R^{10}$ ; -SO,NR  $^{9}R^{10}$ ; -PO(OR  $^{16}$ )OR  $^{17}$ ; -PR  $^{9}R^{10}$ , -P  $^{4}R^{9}R^{11}R^{12}A^{-}$ ; or -S  $^{4}R^{9}R^{10}A^{-}$ ; and

5

wherein in RX, one or more carbons are optionally replaced by -O; - NR <sup>13</sup>-; -N<sup>†</sup>R <sup>13</sup>R <sup>14</sup>A <sup>-</sup>; -S-; -SO-; -SO<sub>2</sub>; -S<sup>†</sup>R <sup>13</sup>A <sup>-</sup>; -P(O)R <sup>13</sup>-; -P<sup>†</sup>R <sup>13</sup>R <sup>14</sup>A <sup>-</sup>; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; and

- wherein in said polyalkyl; phenylene; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue; one or more carbons are optionally replaced by -O:; -NR<sup>9</sup>:, -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A:; -S:; -SO:; -SO2:; -S<sup>+</sup>R<sup>9</sup>A:; -PR<sup>9</sup>:, -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A:; or -P(O)R<sup>9</sup>.
- 35. A compound of claim 33 wherein said one or more R<sup>x</sup> are independently selected from the group consisting of alkyl; aryl; cycloalkyl; heterocyclyl; polyalkyl; acyloxy; polyether; halogen; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; -NR <sup>13</sup>R <sup>14</sup>R <sup>15</sup>; -N<sup>4</sup>R <sup>9</sup>R <sup>11</sup>R <sup>12</sup>A <sup>-</sup>; -SR <sup>13</sup>; -S<sup>4</sup>R <sup>13</sup>R <sup>14</sup>A; -CO<sub>2</sub>R <sup>13</sup>; and -NR <sup>14</sup>C(O)R <sup>13</sup>;
- wherein alkyl; aryl; cycloalkyl; heterocyclyl; polyalkyl; acyloxy; and polyether; can be further substituted with -OR <sup>16</sup>; -NR <sup>9</sup>R <sup>10</sup>; -N<sup>+</sup>R <sup>9</sup>R <sup>10</sup>R <sup>w</sup>A; -SR <sup>16</sup>; -S(O)R <sup>9</sup>; -SO<sub>2</sub>R <sup>9</sup>; -SO<sub>3</sub>R <sup>16</sup>; oxo; -CO<sub>2</sub>R <sup>16</sup>; -CN; halogen; -CONR <sup>9</sup>R <sup>10</sup>; -SO<sub>3</sub>NR <sup>9</sup>R <sup>10</sup>; -PO(OR <sup>16</sup>)OR <sup>17</sup>; -PR <sup>9</sup>R <sup>10</sup>; -P <sup>+</sup>R <sup>9</sup>R <sup>11</sup>R <sup>12</sup>A <sup>7</sup>; or -S <sup>+</sup>R <sup>9</sup>R <sup>10</sup>A <sup>7</sup>; and
- wherein in RX, one or more carbons are optionally replaced by -O-; -NR  $^{13}$ ; -N $^{+}$ R  $^{14}$ A $^{-}$ ; -S-; -SO-; -SO<sub>2</sub>; -S $^{+}$ R  $^{13}$ A-; -PR  $^{13}$ : -P(O)R  $^{13}$ : -

PCT/US00/02503

247

 ${
m P}^+{
m R}^{13}{
m R}^{14}{
m A}^-$ ; phenylene; amino acid residue; peptide residue; polypeptide residue; polyether; or polyalkyl; and

- wherein in said polyalkyl; phenylene; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue; one or more carbons are optionally replaced by -O-; -NR<sup>2</sup>-; -N<sup>+</sup>R<sup>2</sup>R<sup>10</sup>A-; -S-; -SO-; -SO<sub>2</sub>: -S<sup>+</sup>R<sup>2</sup>A-; -PR<sup>2</sup>-; -PR<sup></sup>
- 36. A compound of claim 34 wherein said one or more R\* are independently selected from the group consisting of polyether; -OR  $^{13}$ ; NR  $^{13}R_1^{14}$ ; and -N\*R9R  $^{11}R_1^{12}A$ .
- 37. A compound of the claim 35 wherein said  $R^x$  is selected from the group consisting of polyether, -OR  $^{13}$ ; -NR  $^{13}R^{14}$ ; and -N^R $^{9}R^{11}R^{12}A^{+}$ .
- 38. A compound of claim 36 wherein said one or more R' are independently selected from the group consisting of -OR  $^{13}$  and -NR  $^{13}$ R  $^{14}$
- 39. A compound of claim 37 wherein said  $\rm R^x$  is independently selected from the group consisting of -OR  $^{13}$  and -NR  $^{13}\rm R^{14}$  .
- 40. A compound of claim 38 wherein R<sup>13</sup> and R<sup>14</sup> are each methyl.
- 41. A compound of the claim 39 wherein  $\mathbb{R}^{13}$  and  $\mathbb{R}^{14}$  are each methyl.
- 42. A compound of claim 11 wherein an  $\mathbb{R}^{y}$  substituent is attached at the 3- or the 4-position of the phenyl ring of the structure of formula (II).
- 43. A compound of claim 11 wherein t is 1 or 2.
- 44. A compound of claim 42 wherein t is 1 or 2.
- A compound of claim 11 wherein said one or more R<sup>y</sup> are independently selected from the group consisting of hydrogen; halogen; hydroxy; -NO2; (C,-C<sub>10</sub>)alkyl; halo(C,-C<sub>10</sub>)alkyl; aryl(C,-C<sub>10</sub>)alkyl;

WO 00/47568 PCT/US00/02503

368

heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether, -OR  $^{13}$ ; -NR  $^{13}$ R  $^{14}$ ; and -NR  $^{13}$ C(O)R  $^{14}$ ;

and

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl;

(C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether, or wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quatemary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quatemary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quatemary heterocyclyl; quatemary heterocyclyl; quatemary heterocyclyl; quatemary heterocyclyl; quatemary heterocyclyl; c<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; -OR <sup>16</sup>; -NR <sup>9</sup>R <sup>10</sup>; -N<sup>7</sup>R <sup>9</sup>R <sup>10</sup>; -N<sup>7</sup>R <sup>9</sup>R <sup>10</sup>; and -CONR <sup>9</sup>R <sup>10</sup>; and

wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>w</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxylctarboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and acyl; and

ຊ

wherein A is a pharmaceutically acceptable anion; and
wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group
consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;
carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or
R<sup>11</sup> and R<sup>12</sup> together with the carbon atom to which they are attached

form a cyclic ring; and wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group consisting of  $\mathbb{R}^9$  and  $\mathbb{M}$ ; and

ဓ္က

wherein M is a pharmaceutically acceptable cation.

46. A compound of claim 11 wherein said R<sup>y</sup> is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, hydroxy, methoxy, ethoxy, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium,

trimethylammoniummethylcarbonylamino,

PCT/US00/02503

369

triethylammoniummethylcarbonylamino, trimethylammoniumethylcarbonylamino, triethylammoniumethylcarbonylamino, trimethylammoniumpropylcarbonylamino,

- 10 triethylammoniumpropylcarbonylamino,
  trimethylammoniumbutylcarbonylamino,
  triethylammoniumbutylcarbonylamino, methylcarbonylamino,
  chloromethylcarbonylamino, fluoromethylcarbonylamino,
  bromomethylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino,
- 15 chloroethylcarbonylamino, fluoroethylcarbonylamino, bromoethylcarbonylamino, iodoethylcarbonylamino, propylcarbonylamino, chloropropylcarbonylamino, fluoropropylcarbonylamino, bromopropylcarbonylamino, iodopropylcarbonylamino, butylcarbonylamino, chlorobutylcarbonylamino, fluorobutylcarbonylamino,
- 20 bromobutylcarbonylamino, iodobutylcarbonylamino, methoxycarbonyl, ethoxycarbonyl, trimethylammoniumethoxyethoxyethoxyethoxy, triethylammoniumethoxyethoxy, chloroethoxyethoxyethoxy, fluoroethoxyethoxyethoxy, bromoethoxyethoxyethoxy, iodoethoxyethoxyethoxy, pyridiniumethoxyethoxyethoxy,
- piperazinyloxymethoxyethoxy, methylpiperazinyloxymethoxyethoxyethoxy, dimethylpiperazinyloxymethoxyethoxyethoxy, piperidinyloxymethoxyethoxyethoxy, methylpiperidinyloxymethoxyethoxyethoxy, and dimethylpiperidinyloxymethoxyethoxyethoxyphenyl.

23

30

- 47. A compound of claim 11 wherein said one or more RY are independently selected from the group consisting of hydroxy, methoxy, ethoxy, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium, triethylammonium, triethylammonium, triethylamino,
- trimethylammoniummethylcarbonylamino, triethylammoniummethylcarbonylamino, triethylammoniumethylcarbonylamino, triethylammoniumethylcarbonylamino, triethylammoniumethylcarbonylamino, trimethylammoniumpropylcarbonylamino,

WO 00/47568 PCT/US00/02503

3/0

triethylammoniumpropylearbonylamino,
trimethylammoniumbutylearbonylamino,
triethylammoniumbutylearbonylamino, methylearbonylamino,
chloromethylearbonylamino, fluoromethylearbonylamino,
bromomethylearbonylamino, iodomethylearbonylamino, ethylearbonylamino
tohloroethylearbonylamino, fluoroethylearbonylamino,

bromoethylcarbonylamino, iodoethylcarbonylamino, propylcarbonylamino,

- chloropropylcarbonylamino, fluoropropylcarbonylamino, butylcarbonylamino, bromopropylcarbonylamino, iodopropylcarbonylamino, butylcarbonylamino, chlorobutylcarbonylamino, fluorobutylcarbonylamino, fluorobutylcarbonylamino, bromobutylcarbonylamino, iodobutylcarbonylamino, trimethylammoniumethoxyethoxyethoxy, chloroethoxyethoxyethoxy, fluoroethoxyethoxyethoxyethoxy, bromoethoxyethoxyethoxy, iodoethoxyethoxyethoxy, and pyridiniumethoxyethoxyethoxyethoxy.
- 48. A compound of claim 11 wherein said one or more R<sup>Y</sup> are independently selected from the group consisting of trimethylammonium, triethylammonium, trimethylammoniummethylcarbonylamino, triethylammoniummethylcarbonylamino, trimethylammoniumethylcarbonylamino, triethylammoniumethylcarbonylamino, triithylammoniumethylcarbonylamino, triithylammoniumpropylcarbonylamino, triithylammoniumpropylcarbonylamino, triithylammoniumpropylcarbonylamino, triithylammoniumbutylcarbonylamino, triithylammoniumbutylcarbonylamino, triithylammoniumbutylcarbonylamino, triithylammoniumbutylcarbonylamino,

5

triethylammoniumethoxyethoxyethoxy.

- 49. A compound of claim 11 wherein:
  R<sup>N</sup> is selected from the group consisting of hydrogen, alkyl and aralkyl;
  and
- R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, alkyl, and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl.

PCT/US00/02503 WO 00/47568

371

A compound of claim 11 wherein:

 $\mathbb{R}^N$  is selected from the group consisting of hydrogen, alkyl and aralkyl;

and

R3 and R4 are independently selected from the group consisting of

hydrogen and hydroxy.

S

A compound of claim 50 wherein said hydroxy group is in a syn relationship to said structure of formula (II).

52. A compound of claim 11 wherein:

RN is selected from the group consisting of hydrogen, alkyl and aralkyl;

ઘ

S

 $\mathbb{R}^{\mathsf{X}}$  is selected from the group consisting of polyether, -OR  $^{13}$ ; -NR13R14; and -N+R9R11R12A-;

wherein R9, R11, R12, R13 and R14 are as defined in claim 2.

A compound of claim 11 wherein:

R 1 and R 2 are independently selected from the group consisting of

and R4 are independently selected from the group consisting of hydrogen and hydrogen, alkyl, and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; and hydroxy.

A compound of claim 11 wherein:

is selected from the group consisting of polyether, -OR13; -NR13R14; and -54. A compound of claim 11 whereur.  $R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen, alkyl, and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; and N+R9R11R12A:

wherein R, R11, R12, R13 and R14 are as defined in claim 2.

55. A compound of claim 11 wherein:

R3 and R4 are independently selected from the group consisting of hydrogen and hydroxy; and

RX is selected from the group consisting of polyether; -OR 13; -NR 13R 14; and -N + R9R 11R 12A;

Š

WO 00/47568

PCT/US00/02503

wherein R, R11, R12, R13 and R14 are as defined in claim 2.

A compound of claim 11 wherein:

RN is selected from the group consisting of hydrogen, alkyl and aralkyl; R 1 and R 2 are independently selected from the group consisting of hydrogen, alkyl, and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl; and

and R4 are independently selected from the group consisting of hydrogen and

hydroxy.

R" is selected from the group consisting of hydrogen, alkyl and aralkyl; 57. A compound of claim 11 wherein:

R and R are independently selected from the group consisting of

is selected from the group consisting of polyether, -OR 13; -NR 13R 14; and hydrogen, alkyl, and (C3-C10)cycloalkyl; and N+R9R11R12A:

wherein R, R", R12, R13 and R14 are as defined in claim 2.

58. A compound of claim 11 wherein:

R" is selected from the group consisting of hydrogen, alkyl and aralkyl; R3 and R4 are independently selected from the group consisting of hydrogen and hydroxy; and

RX is selected from the group consisting of polyether; -OR 13; -NR13R14; and .N+R9R11R12A;

wherein R, R1, R12, R13 and R14 are as defined in claim 2.

A compound of claim 11 wherein: 59.

 $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of

R3 and R4 are independently selected from the group consisting of hydrogen, alkyl, and (C3-C10)cycloalkyl;

 $R^{\mathbf{X}}$  is selected from the group consisting of polyether, -OR  $^{13}$ ; hydrogen and hydroxy; and

NR13R14; and -N+R9R11R12A-;

wherein R9, R11, R12, R13 and R14 are as defined in claim 2.

A compound of claim 11 wherein:

WO 00/47568 PCT/US00/02503

373

R<sup>N</sup> is selected from the group consisting of hydrogen, alkyl and aralkyl;
R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of
hydrogen, alkyl, and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl;
R<sup>2</sup> and R<sup>4</sup>
are independently selected from the group consisting of hydrogen and hydroxy;

 $R^X$  is selected from the group consisting of polyether; -OR  $^{13}$  , NR  $^{13}\mathrm{R}^{14}$  ; and -N  $^+\mathrm{R}^9\mathrm{R}^{11}\mathrm{R}^{12}A^-$  ;

wherein R, R, R, R, R, R, and R, are as defined in claim 2.

- 61. A compound of claim 60 wherein R<sup>N</sup> is selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl and aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl.
- 62. A compound of claim 60 wherein R<sup>N</sup> is selected from the group consisting of hydrogen, methyl, ethyl and benzyl.
- 63. A compound of claim 60 wherein  $R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen and  $(C_1 C_{10})$ alkyl.
- 64. A compound of claim 60 wherein  $\mathbb{R}^1$  and  $\mathbb{R}^2$  are independently selected from the group consisting of  $(C_i C_{10})$  alkyl.
- 65. A compound of claim 60 wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl.
- 66. A compound of claim 60 wherein R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting ethyl; n-propyl; n-butyl; and isobutyl.
- 7. A compound of claim 60 wherein R1 and R2 are each n-butyl
- 68. A compound of claim 60 wherein one of  $\mathbb{R}^1$  and  $\mathbb{R}^2$  is ethyl and the other of  $\mathbb{R}^1$  and  $\mathbb{R}^2$  is n-butyl.
- A compound of claim 60 wherein q is 1, 2, or 3.
- 70. A compound of claim 60 wherein q is 1 or 2.

WO 00/47568 PCT/US00/02503

374

- 71. A compound of claim 60 wherein q is 1.
- 72. A compound of claim 60 wherein R<sup>X</sup> radicals are present at the 7-, 8- and 9-positions of the benzo ring of the structure of formula (1).
- 73. A compound of claim 60 wherein an R<sup>X</sup> radical is present at one or more of the 7-, 8-, or 9-positions of the benzo ring of the structure of formula (I).
- 74. A compound of claim 60 wherein R<sup>X</sup> radicals are present at the 7- and 9-positions of the benzo ring of the structure of formula (I).
- 75. A compound of claim 60 wherein an  $\mathbb{R}^X$  radical is present at the 7-position of the benzo ring of the structure of formula (I).
- 76. A compound of claim 60 wherein said one or more R\* are independently selected from the group consisting of -OR  $^{13}$  and -NR  $^{13}$ R  $^{14}$ , wherein R $^{19}$  and R $^{1*}$  are as defined in claim 2..
- 77. A compound of claim 76 wherein  $\mathbb{R}^{13}$  and  $\mathbb{R}^{14}$  are each methyl.
- 78. A compound of claim 60 wherein an R<sup>Y</sup> substituent is independently attached at the 3- or the 4-position of the phenyl ring of formula (II).
- 79. A compound of claim 60 wherein t is 1 or 2.
- 80. A compound of claim 60 wherein t is 1.
- 81. A compound of claim 60 wherein said one or more R<sup>y</sup> are independently selected from the group consisting of hydrogen; halogen; hydroxy; -NO<sub>2</sub>; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; and -NR<sup>13</sup>C(O)R<sup>14</sup>; and

PCT/US00/02503

375

wherein R13, R14, and R15 are independently selected from the group quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quatemary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl;

2

- C<sub>10</sub>)alkyl; quatemary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>heterocyclyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>optionally may be substituted with one or more radicals selected from the heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>wherein the R  $^{13},$  R  $^{14},$  and R  $^{15}$  (C,-C,0)alkyl; halo(C,-C,0)alkyl; C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals C10,0alkyl; -OR16; -NR9R10; -N+R9R10RWA; and -CONR9R10; and group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary (C1-C10)alkylammonium(C1-C10)alkyl; and polyether; or 2
- consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; wherein R9, R10, and RW are independently selected from the group (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxyheterocyclyl; carboxy(C,-C,0)alkylamino; and acyl; and wherein A is a pharmaceutically acceptable anion; and ន
  - wherein R11 and R12 are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or 53
- R11 and R12 together with the carbon atom to which they are attached wherein R16 and R17 are independently selected from the group form a cyclic ring; and

wherein M is a pharmaceutically acceptable cation.

consisting of R9 and M; and

8

- selected from the group consisting of hydrogen, chloro, fluoro, bromo, iodo, A compound of claim 60 wherein said RY is independently hydroxy, methoxy, ethoxy, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium, trimethylammoniummethylcarbonylamino, 82
  - trimethylammoniumethylcarbonylamino, triethylammoniummethylcarbonylamino,

WO 00/47568

PCT/US00/02503

376

trimethylammoniumpropylcarbonylamino, riethylammoniumethylcarbonylamino,

- promomethylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino, triethylammoniumbutylcarbonylamino, methylcarbonylamino, chloromethylcarbonylamino, fluoromethylcarbonylamino, trimethylammoniumbutylcarbonylamino, triethylammoniumpropylcarbonylamino, 2
- bromopropylcarbonylamino, iodopropylcarbonylamino, butylcarbonylamino, promoethylcarbonylamino, iodoethylcarbonylamino, propylcarbonylamino, chloropropylcarbonylamino, fluoropropylcarbonylamino, chlorobutylcarbonylamino, fluorobutylcarbonylamino, chloroethylcarbonylamino, fluoroethylcarbonylamino, 2
- bromobutylcarbonylamino, iodobutylcarbonylamino, methoxycarbonyl, triethylammoniumethoxyethoxyethoxy, chloroethoxyethoxyethoxy, ethoxycarbonyl, trimethylammoniumethoxyethoxy, odoethoxyethoxyethoxy, pyridiniumethoxyethoxy, fluoroethoxyethoxy, bromoethoxyethoxyethoxy, ន 23
  - methylpiperidinyloxymethoxyethoxyethoxy, and dimethylpiperazinyloxymethoxyethoxyethoxy, methylpiperazinyloxymethoxyethoxy, piperidinyloxymethoxyethoxy, piperazinyloxymethoxyethoxyethoxy,

dimethylpiperidinyloxymethoxyethoxyethoxyphenyl.

- independently selected from the group consisting of hydroxy, methoxy, ethoxy, A compound of claim 60 wherein said one or more RY are nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium, 83.
- trimethylammoniummethylcarbonylamino trimethylammoniumpropylcarbonylamino. triethylammoniummethylcarbonylamino, trimethylammoniumethylcarbonylamino, triethylammoniumethylcarbonylamino,
  - trimethylammoniumbutylcarbonylamino, triethylammoniumpropylcarbonylamino, 2

chloropropylcarbonylamino, fluoropropylcarbonylamino, bromoethylcarbonylamino, iodoethylcarbonylamino, propylcarbonylamino, chloroethylcarbonylamino, fluoroethylcarbonylamino,

2

bromobutylcarbonylamino, iodobutylcarbonylamino, bromopropylcarbonylamino, iodopropylcarbonylamino, butylcarbonylamino chlorobutylcarbonylamino, fluorobutylcarbonylamino,

20

triethylammoniumethoxyethoxyethoxy, chloroethoxyethoxyethoxy, trimethylammoniumethoxyethoxy, iodoethoxyethoxy, and pyridiniumethoxyethoxyethoxy. fluoroethoxyethoxyethoxy, bromoethoxyethoxyethoxy,

triethylammoniummethylcarbonylamino, triethylammonium, trimethylammoniummethylcarbonylamino, independently selected from the group consisting of trimethylammonium, A compound of claim 60 wherein said one or more RY are

trimethylammoniumethoxyethoxyethoxy, and triethylammoniumbutylcarbonylamino, trimethylammoniumbutylcarbonylamino, triethylammoniumethylcarbonylamino, trimethylammoniumethylcarbonylamino, triethylammoniumpropylcarbonylamino, trimethylammoniumpropylcarbonylamino,

5

triethylammoniumethoxyethoxyethoxy.

relationship to said structure of formula (II) A compound of claim 60 wherein said hydroxy group is in a syn

86. A compound of formula (I):

WO 00/47568

PCT/US00/02503

378

3

5

5

R and R are each independently alkyl; R3 is hydroxy; q is 1 or 2; R4 and R6 are hydrogen;

R<sup>3</sup> has the formula (II):

20

25

wherein t is an integer from 0 to 5;

30

NR<sup>13</sup>SO,NR<sup>14</sup>R<sup>15</sup>,-P(O)R<sup>13</sup>R<sup>14</sup>,-PR<sup>13</sup>R<sup>14</sup>,-P<sup>4</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>;-P(OR<sup>13</sup>)OR<sup>14</sup>,-S<sup>4</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>; and -N<sup>4</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; and OC(O)NR13R14; -NR13SOR14; -NR13SO,R14; -NR13SONR14R15; -CO2R13; -OM; -SO2OM; -SO2NR13R14; -C(O)NR13R14; -C(O)OM; hydroxyalkyt; cycloalkyt; alkenyt; alkynyt; aryt; heterocyclyt; quaternary heterocyclyl; arylalkyt; heterocyclylalkyt; polyether; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>, SR <sup>13</sup>; -SO<sub>2</sub>R <sup>13</sup>; -SO<sub>3</sub>R <sup>13</sup>; -NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -COR<sup>13</sup>; -NR<sup>13</sup>C(O)R<sup>14</sup>; -NR<sup>13</sup>C(O)NR<sup>14</sup>R<sup>13</sup>; -NR<sup>13</sup>CO,R<sup>14</sup>; -OC(O)R<sup>13</sup>; hydrogen; halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; one or more RY are independently selected from the group consisting of

႘

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkenyl, arkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R<sup>Y</sup> radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR?; -NR<sup>7</sup>R<sup>8</sup>; -SR<sup>7</sup>; -SOOR<sup>7</sup>; -SOOR<sup>7</sup>; -SOOR<sup>7</sup>; -CONR<sup>7</sup>R<sup>8</sup>; -R<sup>7</sup>R<sup>8</sup>; -P<sup>7</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A<sup>7</sup>; and -P(O)(OR<sup>7</sup>)OR<sup>8</sup>; and

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, 50 alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R<sup>Y</sup> radicals optionally may have one or more carbons replaced by -O.; -NR<sup>7</sup>; -N<sup>\*</sup>R<sup>3</sup>R<sup>4</sup>··, SS·; -SO·; SO<sub>2</sub>··, S<sup>\*</sup>R<sup>7</sup>A··; -PR<sup>7</sup>·, -P(O)R<sup>7</sup>·, -P<sup>\*</sup>R<sup>7</sup>R<sup>8</sup>A··; or phenylene; and

wherein R<sup>7</sup> and R<sup>8</sup> are independently selected from the group
55 consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and
wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group
consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl;
alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;
heterocyclylalkyl; quaternary heterocyclyl; alkylarylalkyl;

alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or wherein R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;

8

and quaternary salts; or wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylarylalkyl; alkylarylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; acarboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl;

8

WO 00/47568

PCT/US00/02503

380

hydroxyalkyi; sulfoalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary heterocyclyi; quaternary heterocyclyii; carboxy; carboxyalkyi; guaniqinyi; .OR 16; .NR 9R 10; .N + R 9R 10; .N + R 9R 10; .SR 16; .S(O)R 9; .SO2R 9; .SO3R 16; .CO2R 16; .CONR 9R 10; .SO2NR 9R 10; .PO(OR 16)OR 17; .PR 9R 10; .P+ 9R 9R 10; .P+ 9R

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> alkyi; haloalkyi; cycloalkyi; polyalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary heterocyclyi; aryialkyi; heterocyclylalkyi; alkyiaruany heterocyclylalkyi; alkyiaruanyi; alkyiaruanyi, alkyiaruanyi; alkyiaruanyi; anaroxyalkyiaruanyi; alkyiaruanyi; carboxyalkyiaruinocarbonylalkyi; alkyiaruinocarbonylalkyi; alkyiaruinocarbonylalkyii; alkyiaruinocarbonylalkyii; alkyiaruinocarbonylalkyii; alkyiaruinocarbonylalkyii; a

phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and  $\begin{array}{c} \text{polypeptide residue; and} \\ \text{wherein R}^{16} \text{ and R}^{17} \text{ are independently selected from the group consisting of R}^{9} \text{ and M; and} \end{array}$ 

8

wherein M is a pharmaceutically acceptable cation; and wherein R°, R°, R°, R°, R°, and A⁻ are as defined in claim 2; and RN is selected from the group consisting of hydrogen; alkyl; and aralkyl; and

one or more  $\mathbb{R}^X$  radicals are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino; or

95

a pharmaceutically acceptable salt, solvate, or prodrug thereof

87. A compound of claim 86 wherein  $R^1$  and  $R^2$  are each the same ( $C_1$ - $C_1$ -)alkyl.

88. A compound of claim 86 wherein R1 and R2 are each n-butyl.

89. A compound of claim 86 wherein one or more R\* are independently selected from the group consisting of methoxy and dimethylamino.

90. A compound of claim 86 wherein q is 1.

group consisting of methoxy and dimethylamino. 91. A compound of claim 86 wherein q is 1, and R\* is selected from the

- consisting of hydrogen; methyl, ethyl and benzyl. 92. A compound of claim 86 wherein  $\mathbb{R}^{N}$  is selected from the group
- relationship to said structure of formula (II). A compound of claim 86 wherein said hydroxy group is in a syn
- 94. A compound of claim 86 wherein t is 1.
- position. 95. A compound of claim 86 wherein t is 1 and R' is in the para
- position. 96. A compound of claim 86 wherein t is 1 and RY is in the meta
- polyether, -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>, and -NR <sup>13</sup>C(O)R <sup>14</sup>; and wherein R <sup>13</sup>, R <sup>14</sup>, and R <sup>15</sup> are independently selected from the group (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; selected from selected from the group consisting of halogen; hydroxy; -NO2: 97. A compound of claim 86 wherein one or more R' are independently
- quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkylheterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl;
- 5 5 group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary  $C_{ip}$ alkyl; -OR  $^{16}$ ; -NR  $^{9}$ R  $^{10}$ ; -N $^{+}$ R  $^{9}$ R  $^{10}$ R  $^{w}$ A  $^{-}$ ; and -CONR  $^{9}$ R  $^{10}$ ; and heterocyclyl; quaternary heterocyclyl(C1-C10)alkyl; carboxy; carboxy(C1optionally may be substituted with one or more radicals selected from the C10)alkyl; (C1-C10)alkylammonium(C1-C10)alkyl; and polyether radicals  $C_{10}) alkyl; \ quaternary \ heterocyclyl(C_1-C_{10}) alkyl; \ (C_1-C_{10}) alkylheterocyclyl(C_1-C_{10}) alkyli) \ description of the control of the con$ heterocyclyl; quaternary heterocyclyl; aryl(C1-C10)alkyl; heterocyclyl(C1-(C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether; or wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl;

WO 00/47568 PCT/US00/02503

20 (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxyheterocyclyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylamino; and acyl; and C10)alkyl; carboxy(C1-C10)alkyl; carbo(C1-C10)alkoxy(C1-C10)alkyl; wherein  $A^\top$  is a pharmaceutically acceptable anion; and wherein  $R^{11}$  and  $R^{12}$  are independently selected from the group wherein  $\mathbb{R}^9$ ,  $\mathbb{R}^{10}$ , and  $\mathbb{R}^w$  are independently selected from the group

- 25  ${\rm carboxy}(C_i\text{-}C_{i0}) alkyl; \ and \ {\rm carbo}(C_i\text{-}C_{i0}) alkoxy(C_i\text{-}C_{i0}) alkyl; \ or \\ R^{11} \ and \ R^{12} \ together \ with \ the \ carbon \ atom \ to \ which \ they \ are \ attached$ consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; form a cyclic ring; and wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group
- consisting of R9 and M; and wherein M is a pharmaceutically acceptable cation

3

one or more R\* are independently selected from the group consisting of R1 and R2 are each the same (C1-C10) alkyl; 98. A compound of claim 97 wherein:

said hydroxy group is in a syn relationship to said structure of formula

methoxy and dimethylamino;

t is 1; and

Ry is in the meta or para position

- 99. A compound of claim 97 wherein R1 and R2 are each n-butyl.
- 100. A compound of claim 97 wherein q is 1.
- consisting of hydrogen; methyl, ethyl and benzyl. 101. A compound of claim 97 wherein RN is selected from the group
- A compound of claim 97 wherein RY is in the para position.
- 103. A compound of claim 97 wherein RY is in the meta position.

PCT/US00/02503

8

104. A compound of the formula (III):

wherein:

q and r are independently integers from 0 to 4; t and u are independently integers from 0 to 4;

R<sup>1</sup>, R<sup>2</sup>, R<sup>1A</sup>, and R<sup>2A</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkyl; aryloxyalkyl; aryloxyalkyl; aryloxyalkyl; aryloxyalkenyl; heterocyclyloxyalkyl; heterocycloxyalkyl; aryloxyalkenyl; heterocyclyloxyalkyl; alkylaryl; and (polyalkyl)aryl; or

2

 $R^1$  and  $R^2$  taken together with the carbon to which they are attached 15 form C<sub>3</sub>-C<sub>10</sub> cycloalkenyl; or

 $R^{1A}$  and  $R^{2A}$  taken together with the carbon to which they are attached form C,-C<sub>10</sub> cycloalkyl or C,-C<sub>10</sub> cycloalkenyl; wherein the  $R^1$ ,  $R^2$ ,  $R^1$ A, and  $R^{2A}$  alkyl; cycloalkyl; alkenyl;

cycloalkenyl; alkynyl; aryl; heterocyclyl; arylatkyl; heterocyclylalkyl;

alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl;

aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl;

heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may
be substituted with one or more radicals selected from the group consisting of
CN; halogen; oxo; -OR9; -NR9R10; -N+R9R10RWA; -SR9; -S'RRPIOK; -

WO 00/47568

786

25 PR<sup>9</sup>R<sup>10</sup>; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>\*</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; and CONR<sup>9</sup>R<sup>10</sup>; and

wherein the R<sup>1</sup>, R<sup>2</sup>, R<sup>1A</sup>, and R<sup>2A</sup> alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylialkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkyl; aryloxyalkyl; aryloxyalkyl; aryloxyalkyl; aryloxyalkyl; aryloxyalknyl;

30 aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may have one or more carbons replaced by -O.; -NR<sup>9</sup>; -N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-; -S.; -SO.; -SO2-; -S<sup>†</sup>R<sup>9</sup>A-: -PR<sup>9</sup>; -P(O)R<sup>9</sup>; -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-; or phenylene; and wherein R<sup>9</sup>, R<sup>10</sup>, and R<sup>W</sup> are independently selected from the group

consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; arkoxyalkyl; carboxyalkyl; carboxyalkyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; alkoxyalkylamino; alkoxyalkylamino; and acyl; and

wherein A is a pharmaceutically acceptable anion; and R<sup>3</sup>, R<sup>4</sup>, R<sup>3A</sup>, and R<sup>4A</sup> are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; or R<sup>3</sup> and R<sup>4</sup> together form =O, =NOR<sup>9</sup>; =S; =NNR<sup>9</sup>R<sup>10</sup>; =NR<sup>9</sup>; or

<del>6</del>

=CR  $^{11}$ R  $^{12}$ ; or R  $^{34}$  together form =O; =NOR $^9$ ; =S; =NNR $^9$ R  $^{10}$ ; =NR $^9$ ; or =CR  $^{11}$ R  $^{12}$ ;

5

wherein R <sup>11</sup> and R <sup>12</sup> are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; 50 carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cycloalkyl; cycloalkyl; hydroxyalkyl; cycloalkyl; -SN<sup>2</sup> -SO<sub>2</sub>R <sup>2</sup>; -SO<sub>3</sub>R <sup>2</sup>; -CO<sub>2</sub>R <sup>2</sup>; and

-CONR  $^9R^{10}$ ; or  $R^{11}$  and  $R^{12}$  together with the carbon atom to which they are attached form a cyclic ring; and

wherein R° and R¹º are as defined above; and

55

one or more R<sup>y</sup> and R<sup>yA</sup> are independently selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>,

WO 00/47568 PCT/US00/02503

385

60 SR<sup>13</sup>; -S(O)R<sup>13</sup>, -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -NR<sup>12</sup>C(O)R<sup>11</sup>; -NR<sup>12</sup>C(O)R<sup>11</sup>; -NR<sup>12</sup>CO<sub>2</sub>R<sup>11</sup>; -NR<sup>12</sup>CO<sub>3</sub>R<sup>11</sup>; -NR<sup>13</sup>SO<sub>3</sub>R<sup>11</sup>; -NR<sup>13</sup>SO<sub>3</sub>R<sup>11</sup>; -NR<sup>13</sup>SO<sub>3</sub>R<sup>11</sup>; -PR<sup>13</sup>R<sup>14</sup>; -PR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -NR<sup>13</sup>SO<sub>3</sub>NR<sup>11</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -NR<sup>13</sup>SO<sub>3</sub>NR<sup>11</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -NR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -NR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>R<sup>15</sup>R<sup>14</sup>

65 P(OR <sup>13</sup>)OR <sup>14</sup>; S<sup>+</sup>R <sup>13</sup>R <sup>14</sup>A<sup>-</sup>; and -N<sup>+</sup>R <sup>13</sup>R <sup>14</sup>R <sup>15</sup>A<sup>-</sup>; and wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R<sup>y</sup> and R<sup>yA</sup> radicals

optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR; -NR<sup>7</sup>R<sup>8</sup>; -SR<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -CO<sub>2</sub>R<sup>7</sup>; -CO<sub>3</sub>R<sup>7</sup>; -N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A; -P(O)R<sup>7</sup>R<sup>8</sup>; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A; and -P(O)(OR<sup>7</sup>)OR<sup>8</sup>; and

8

wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R<sup>y</sup> and R<sup>yA</sup> radicals optionally may have one or more carbons replaced by -O-; -NR<sup>7</sup>-; -N<sup>†</sup>R<sup>7</sup>R<sup>8</sup>A· -; -SO-; -SO<sub>2</sub>-; -S<sup>†</sup>R<sup>7</sup>A·-; -PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>†</sup>R<sup>7</sup>R<sup>8</sup>A·-; or phenylene; and

7

80

wherein R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl;

8

alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; and polyether; or wherein R¹¹ and R¹¹ together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy,

8

wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are attached form a cyclic ring; and

and quaternary salts; or

· WO 00/47568 PCT/US00/02503

386

ន 8 છ CO2R  $^{16}$  , CONR  $^{9}$ R  $^{10}$  , -SO2NR  $^{9}$ R  $^{10}$  , -PO(OR  $^{16}$ )OR  $^{17}$  , -pR  $^{9}$ R  $^{10}$  , -PR  $^{9}$ R  $^{10}$ A-; -S  $^{4}$ R  $^{9}$ R  $^{10}$ A-; and carbohydrate residue; and -OR16; -NR9R10; -NTR9R10RWA; -SR16; -S(0)R9; -SO2R9; -SO3R10; heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; hydroxyalkyi; sulfoalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; radicals optionally may be substituted with one or more radicals selected from alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl; wherein the  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl;

alkylheterocyclylalkyl; alkylarnmoniumalkyl; aminocarbonylalkyl; alkylarnmoniumalkyl; aminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR<sup>3</sup>-; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; -S-; -SO<sub>2</sub>-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A-; -P(O)R<sup>9</sup>-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

wherein  $\mathbb{R}^{16}$  and  $\mathbb{R}^{17}$  are independently selected from the group consisting of  $\mathbb{R}^9$  and M; and

wherein n is 0, 1 or 2; and

wherein M is a pharmaceutically acceptable cation; and wherein R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>12</sup>, and A<sup>-</sup> are as defined above; and R<sup>N</sup> and R<sup>NA</sup> are independently selected from the group consisting of

hydrogen; alkyl; alkenyl; alkynyl; aralkyl; and heterocyclylalkyl; and

one or more  $\mathbb{R}^{X}$  and  $\mathbb{R}^{X_A}$  radicals are independently selected from the

120

group consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl;

polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl;

uaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy; 
OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>, -SR <sup>13</sup>; -S(O)R <sup>13</sup>; -S(O)R <sup>13</sup>; -SO3R <sup>13</sup>; -S <sup>14</sup>R <sup>14</sup>R <sup>14</sup>A; 
NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -CO2R <sup>13</sup>; -OM; -SO2OM; -SO2NR <sup>13</sup>R <sup>14</sup>; 
NR <sup>16</sup>C(O)R <sup>13</sup>; -C(O)NR <sup>13</sup>R <sup>14</sup>; -C(O)OM; -COR <sup>13</sup>; -OR <sup>18</sup>; -SO<sub>B</sub>NR <sup>13</sup>R <sup>18</sup>; -

387

NR  $^{18}$ OR  $^{14}$ ; N $^{14}$ R  $^{13}$ R  $^{14}$ K  $^{15}$ A $^{1}$ ; -PR  $^{13}$ R  $^{14}$ ; -PR  $^{13}$ R  $^{14}$ R  $^{15}$ A $^{1}$ ; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

135

wherein the R<sup>X</sup> and R<sup>XA</sup> quaternary heterocyclyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether, -OR 1<sup>3</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR 1<sup>3</sup>; -S(O)R 1<sup>3</sup>; -SO2R 1<sup>3</sup>; -SO3R 1<sup>3</sup>; -NR<sup>13</sup>OR 1<sup>4</sup>; -NR 1<sup>3</sup>NR 1<sup>4</sup>K; -CO2R 1<sup>3</sup>; -NO3R 1<sup>3</sup>R 1<sup>4</sup>; -R 1<sup>3</sup>R 1<sup>4</sup>K; -P 1<sup>3</sup>R 1<sup>4</sup>K; and carbohydrate residue; and

wherein the R<sup>x</sup> and R<sup>xx</sup> radicals comprising carbon optionally may lave one or more carbons replaced by -O.; -NR<sup>13</sup>; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A·; -S·; -SO.; -SO<sub>2</sub>·; -S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>·; -PR<sup>13</sup>·; -P(O)R<sup>13</sup>·; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A·; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O·; -NR<sup>9</sup>·; -N<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·; -S·; -SO·; -SO<sub>2</sub>·; -S<sup>+</sup>R<sup>9</sup>A·; -PR<sup>9</sup>·; -P<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A·; or -P(O)R<sup>9</sup>·; and

wherein R <sup>18</sup> is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and

8

wherein the R<sup>14</sup> alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may be substituted with one or more radicals selected from the group consisting of

WO 00/47568

PCT/US00/02503

388

halogen; -CN; NO<sub>2</sub>, oxo; -OR<sup>2</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; -PR<sup>9</sup>R<sup>10</sup>; -P(OR<sup>16</sup>)OR<sup>17</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; and -C(O)OM; and

165

 alkyne diyl; polyalkane diyl; alkoxy diyl; polyether diyl; polyalkoxy diyl; alkyne diyl; polyalkane diyl; alkoxy diyl; polyether diyl; polyalkoxy diyl; carbohydrate; amino acid; and peptide; polypeptide; wherein alkane diyl; alkene diyl; alkene diyl; polyalkane diyl; alkoxy diyl; polyether diyl; polyalkoxy diyl; carbohydrate residue; amino acid residue; peptide residue; and polyalkoxy diyl; carbohydrate residue; amino acid residue; peptide residue; and polypeptide residue; can optionally have one or more carbons replaced by -O-; -NR<sup>7</sup>; -N<sup>4</sup>R<sup>7</sup>R<sup>8</sup>A-; -S.; -SO-; -SO<sub>2</sub>; -S<sup>4</sup>R<sup>7</sup>A-; -PR<sup>7</sup>; -PR<sup>7</sup>R<sup>8</sup>A-; phenylome; heterocyclyl; quaternary heterocyclyl; or aryl;

wherein alkane diyl; alkene diyl; alkyne diyl; polyalkane diyl; alkoxy diyl; polyelher diyl; polyalkoxy diyl; carbohydrate residue; amino acid residue; peptide residue; and polypeptide residue can be substituted with one or more substituted troups independently selected from the group consisting of alkyl; alkenyl; alkynyl; polyalkyl; polyether, aryl; haloalkyl; cycloalkyl; heterocyclyl; arylalkyl; halogen, oxo; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>, -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>, -NR<sup>13</sup>R<sup>14</sup>, -NO<sub>2</sub>; -CO<sub>2</sub>R<sup>13</sup>; -CN; -OM; -

180

185 SO2OM; -SO2NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; -PR<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>; -P(OR<sup>13</sup>)OR"; -S'R<sup>13</sup>R<sup>14</sup>A; and -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>;

wherein R', R', R', R', R', R', R', and A' are as defined above; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

- 105. A compound of claim 104 wherein  $R^1$ ,  $R^{14}$ ,  $R^2$ , and  $R^{24}$  are independently selected from the group consisting of bydrogen and alkyl.
- 106. A compound of claim 104 wherein R¹, R¹, R², and R², are independently selected from the group consisting of hydrogen and C₁-C₁₀ alkyl.
- 107. A compound of claim 104 wherein R¹, R¹A, R², and R²A are independently selected from the group consisting of C₂-C₂ alkyl.

PCT/US00/02503

68E

- 108. A compound of claim 104 wherein R<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup>, and R<sup>2</sup> are independently selected from the group consisting of C<sub>2</sub>-C<sub>4</sub> alkyl.
- 109. A compound of claim 104 wherein R¹, R¹, R³, and R²^ are independently selected from the group consisting of ethyl; n-propyl; n-butyl; and isobutyl.
- 110. A compound of claim 104 wherein R³, R³, R⁴, and R⁴ are independently selected from the group consisting of hydrogen and -OR³, wherein R³ is as defined in claim 104.
- 111. A compound of claim 110 wherein R9 is hydrogen.
- 112. A compound of claim 104 wherein R<sup>N</sup> and R<sup>NA</sup> are independently selected from the group consisting of hydrogen, alkyl and aralkyl.
- 113. A compound of claim 104 wherein R<sup>N</sup> and R<sup>NN</sup> are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl and aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl.
- 114. A compound of claim 104 wherein R<sup>N</sup> and R<sup>NA</sup> are independently selected from the group consisting of hydrogen, methyl, ethyl and benzyl.
- 115. A compound of claim 104 wherein one or more R\* and R\*\* are independently selected from the group consisting of methoxy and dimethylamino.
- 116. A compound of claim 104 wherein q and r are each 1.
- 117. A compound of claim 104 wherein one or more R<sup>y</sup> are independently selected from selected from the group consisting of halogen; hydroxy; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;

WO 00/47568 PCT/US00/02503

390

heterocyclyi(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; and -NR <sup>13</sup>C(O)R <sup>14</sup>; and

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether; or

5

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals

optionally may be substituted with one or more radicals selected from the group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl; C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; -OR <sup>16</sup>, -NR <sup>9</sup>R <sup>10</sup>, -N <sup>4</sup>R <sup>9</sup>R <sup>10</sup>R <sup>4</sup>M <sup>2</sup>; and -CONR <sup>9</sup>R <sup>10</sup>; and wherein R <sup>9</sup>, R <sup>10</sup>, and R <sup>4</sup>W are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl;

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or R<sup>11</sup> and R<sup>12</sup> together with the carbon atom to which they are attached form a cyclic ring

carboxyheterocyclyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylamino; and acyl; and

wherein A is a pharmaceutically acceptable anion; and

wherein  $R^{16}$  and  $R^{17}$  are independently selected from the group consisting of  $R^9$  and M; and wherein M is a pharmaceutically acceptable cation.

118. A compound of claim 104 wherein  $\mathbb{R}^{19}$  is selected from the group consisting of alkane diyl; polyalkane diyl; alkoxy diyl; and polyalkoxy

diyl; wherein alkane diyl and polyalkane diyl can optionally have one or more carbons replaced by -O;  $-NR^7$ ;  $-N^+R^7R^8A$ ; -S; -SO; -SO;  $-S^+R^7A$ ; -

PCT/US00/02503

102

5  $PR^7$ ; -P(O)R $^7$ : -P $^4R^7R^8A$ : or phenylene, wherein R $^7$  and R $^4$  are defined as in claim 104.

119. A compound of claim 104 wherein  $R^{19}$  is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by -O<sub>7</sub>: -NR<sup>7</sup>.: N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup>; -S·-SO<sub>2</sub>: -SO<sub>2</sub>: -S<sup>\*</sup>R<sup>7</sup>A<sup>-</sup>; -PR<sup>7</sup>; -P(O)R<sup>7</sup>; -P<sup>\*</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup>; phenylene; amino acid residue;

wherein R° and R¹º are defined as in claim 104.

A compound of claim 104 having the formula:

peptide residue; polypeptide residue; carbohydrate residue; or polyalkyl,

121. A compound of the formula (IV):

WO 00/47568

PCT/US00/02503

392

wherein

q and r are independently integers from 0 to 3; t and u are independently integers from 0 to 5; R<sup>1</sup>, R<sup>2</sup>, R<sup>1A</sup>, and R<sup>2A</sup> are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; eycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclyl; arylalkyl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkenyl;

20 alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl; or

 $R^1$  and  $R^2$  taken together with the carbon to which they are attached form  $C_3\text{-}C_{10}$  cycloalkyl or  $C_3\text{-}C_{10}$  cycloalkyl or  $C_3\text{-}C_{10}$ 

25 R<sup>1A</sup> and R<sup>2A</sup> taken together with the carbon to which they are attached form C<sub>1</sub>-C<sub>10</sub> eycloalkyl or C<sub>3</sub>-C<sub>10</sub> eycloalkenyl; wherein the R<sup>1</sup>, R<sup>2</sup>, R<sup>1A</sup>, and R<sup>2A</sup> alkyl; cycloalkyl; alkenyl;

cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl;

alkoxyalkyi; alkoxyalkenyl; alkoxyalkynyi; aryloxyalkyi; aryloxyalkenyl;

aryloxyalkynyl; heterocylcyloxyalkyi; heterocycloxyalkenyl;
heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may
be substituted with one or more radicals selected from the group consisting ofCN; halogen; oxo; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>4</sup>R<sup>9</sup>R<sup>10</sup>R<sup>M-1</sup>; -SR<sup>9</sup>; -SR<sup>9</sup>R<sup>10</sup>, -P<sup>4</sup>R<sup>9</sup>R<sup>10</sup>, -P<sup>4</sup>R<sup>9</sup>R<sup>10</sup>, -P<sup>4</sup>R<sup>9</sup>R<sup>10</sup>, -P<sup>4</sup>R<sup>9</sup>R<sup>10</sup>, -SO<sup>2</sup>R<sup>9</sup>; -SO<sub>3</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; and -

35 CONR 9R 10; and

aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; wherein the  $R^1$ ,  $R^2$ ,  $R^{1A}$ , and  $R^{2A}$  alkyl; cycloalkyl; alkenyl;

 $SO_{2}$ ;  $-S^{\dagger}R^{9}A^{-}$ ;  $-PR^{9}$ ;  $-P(O)R^{9}$ ;  $-P^{\dagger}R^{9}R^{10}A^{-}$ ; or phenylene; and have one or more carbons replaced by -O-; -NR 9-; -N R 9R 10A-; -S-; -SO-; heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may wherein  $\mathbb{R}^9$ ,  $\mathbb{R}^{10}$ , and  $\mathbb{R}^w$  are independently selected from the group

6

carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; carboxyalkylamino; alkoxyalkylamino; and acyl; and

3

 $\mathbb{R}^3$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^{3A}$ , and  $\mathbb{R}^{4A}$  are independently selected from the group wherein A is a pharmaceutically acceptable anion; and

consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; or R3 and R4 together form =O; =NOR9; =S; =NNR9R10; =NR9; or

S

 $=CR^{11}R^{12};$  $R^{3A}$  and  $R^{4A}$  together form =0; =NOR<sup>9</sup>; =S; =NNR<sup>9</sup>R<sup>10</sup>; =NR<sup>9</sup>; or

S

cyanoalkyl; -OR2; -NR2R10; -SR2; -S(O)R2; -SO2R2; -SO3R2; -CO2R2; and carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; wherein  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  are independently selected from the group

8

form a cyclic ring; and -CONR<sup>9</sup>R<sup>10</sup>; or  ${
m R}^{11}$  and  ${
m R}^{12}$  together with the carbon atom to which they are attached

wherein R9 and R10 are as defined above; and

ಜ 8 heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>, -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -SO<sub>2</sub>R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO2R 13; -OM; -SO2OM; -SO2NR 13R 14; -C(O)NR 13R 14; -C(O)OM; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary consisting of hydrogen; halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; one or more  $R^{y}$  and  $R^{yA}$  are independently selected from the group

> WO 00/47568 PCT/US00/02503

P(OR 13)OR 14; -S+R 13R 14A; and -N+R 13R 14R 15A; and NR"SO,NR"R"; -P(O)R 13R 14; -PR 13R 14; -P+R 13R 14R 15A; -OC(O)NR13R14; -NR13SOR14; -NR13SO,R14; -NR13SONR14R15; -COR<sup>13</sup>; -NR<sup>13</sup>C(0)R<sup>14</sup>; -NR<sup>13</sup>C(0)NR<sup>14</sup>R<sup>15</sup>; -NR<sup>13</sup>CO<sub>2</sub>R<sup>14</sup>; -OC(0)R<sup>15</sup>; -

겅

alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR<sup>7</sup>; -NR<sup>7</sup>R<sup>8</sup>; -SR<sup>7</sup>; -S(O)R<sup>7</sup>; -SO<sub>2</sub>R<sup>7</sup>; -SO<sub>3</sub>R<sup>7</sup>; -CO<sub>2</sub>R<sup>7</sup>; -CO<sub>2</sub>R<sup>7</sup>; -CO<sub>2</sub>R<sup>7</sup>; -PR<sup>7</sup>R<sup>8</sup>; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>R<sup>9</sup>A<sup>7</sup>; and -P(O)(OR<sup>7</sup>)OR<sup>8</sup>; and heterocyclylalkyl, and polyether substituents of the RY and RYA radicals the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; optionally may be further substituted with one or more radicals selected from alkenyi, alkynyi, aryi, heterocyclyi, quaternary heterocyclyi, aryialkyi, wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl

80

 $\cdot$ ;  $\cdot$ So-;  $\cdot$ SO2-;  $\cdot$ S<sup>†</sup>R<sup>7</sup>A-;  $\cdot$ PR<sup>7</sup>-;  $\cdot$ P(O)R<sup>7</sup>-;  $\cdot$ P<sup>†</sup>R<sup>7</sup>R<sup>8</sup>A-; or phenylene; optionally may have one or more carbons replaced by -O-; -NR -; -N+R 7R 8Aalkenyi, alkynyi, aryi, heterocyclyi, quaternary heterocyclyi, aryialkyi, heterocyclylalkyl, and polyether substituents of the RY and RYA radicals wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl

8

જ છ consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and alkynyi; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; wherein  $\mathbb{R}^{13}$ ,  $\mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the group wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group

alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; attached form a mono- or polycyclic heterocyclyl that is optionally substituted heterocyclylalkyl; quatemary heterocyclylalkyl; alkylarylalkyl; wherein R13 and R14 together with the nitrogen atom to which they are

8 with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or wherein  $\mathbb{R}^{14}$  and  $\mathbb{R}^{15}$  together with the nitrogen atom to which they are

alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; attached form a cyclic ring; and wherein the R <sup>13</sup>, R <sup>14</sup>, and R <sup>15</sup> alkyl; haloalkyl; cycloalkyl; polyalkyl;

ខ្ល

heterocyclyl, quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl;  $-OR^{16}$ ;  $-NR^{9}R^{10}$ ,  $-N^{*}R^{9}R^{11}R^{12}A$ ;  $-SO^{16}$ ;  $-SO^{9}R^{9}$ ;  $-SO_{3}R^{16}$ ;  $-SO_{3}R^{$ radicals optionally may be substituted with one or more radicals selected from alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary CO2R 16; -CONR 9R 10; -SO2NR 9R 10; -PO(OR 16) OR 17; -PR 9R 10; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; 2

wherein the R  $^{13}$ , R  $^{14}$ , and R  $^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; alkylheterocyclylalkyl; alkylarmoniumalkyl; aminocarbonylalkyl; heterocyclytalkyl; quaternary heterocyclytalkyl; alkylarytalkyl; P+R9R10R11A-; -S+R9R10A-; and carbohydrate residue; and

≃

N+R9R10A:: -S:, -SO:, -SO2:, -S+R9A:-, -PR9-, -P+R9R10A:; -P(O)R9.; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR9-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and 20

wherein R 16 and R 17 are independently selected from the group wherein M is a pharmaceutically acceptable cation; and wherein n is 0, 1 or 2; and consisting of R9 and M; and

125

one or more RX and RXA radicals are independently selected from the  $R^{N}$  and  $R^{\mathsf{NA}}$  are independently selected from the group consisting of wherein R, R10, R11, R12, R, and A are as defined above; and hydrogen; alkyl; alkenyl; alkynyl; aralkyl; and heterocyclylalkyl; and 130

OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; -SR<sup>13</sup>; -S(O)R<sup>13</sup>; -S(O)2R<sup>13</sup>; -SO<sub>3</sub>R<sup>13</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sub>\*</sub>; -NR<sup>13</sup>OR<sup>14</sup>, -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, -CO<sub>2</sub>R<sup>13</sup>, -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, -NR<sup>13</sup>OR<sup>14</sup>, -C(O)NR<sup>13</sup>R<sup>14</sup>, -C(O)OM; -COR<sup>13</sup>, -OR<sup>18</sup>, -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>, NR<sup>18</sup>OR<sup>14</sup>, -N<sup>4</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -P(O)R<sup>13</sup>R<sup>14</sup>; -P(O)R<sup>13</sup>R<sup>14</sup>; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether, acyloxy; polyalkyi; haloalkyi; hydroxyalkyi; alkenyi; alkynyi; aryi; heterocyclyi; group consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl;

135

PCT/US00/02503

 $\mathbf{p}^+\mathbf{R}^{13}\mathbf{R}^{14}\mathbf{R}^{15}\mathbf{A}^-$  ; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue; 40

more radicals selected from the group consisting of halogen; -CN; oxo; -OR16, -NR9R10; -N<sup>+</sup>R9R10R<sup>W</sup>A<sup>-</sup>; -SR<sup>16</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>16</sup>; -CO<sub>2</sub>R<sup>16</sup>; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; CONR 9R 10; -SO2NR 9R 10; -PO(OR ")OR"; -PR 9R 10; -P-R 9R 11R 12A-; polyether; acyloxy radicals optionally may be further substituted with one or wherein the RX and RXA alkyl; cycloalkyl; polyalkyl; haloalkyl; S+R9R10A; and carbohydrate residue; and 145

hydroxyalkyl; alkenyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether;  $-OR^{13}$ ,  $-NR^{13}R^{14}$ ,  $-SR^{13}$ ,  $-S(O)R^{13}$ ,  $-SO_2R^{13}$ ,  $-SO_3R^{13}$ , . wherein the RX and RXA quaternary heterocyclyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; 150

C(0)NR<sup>13</sup>R<sup>14</sup>,-C(0)OM; -COR<sup>13</sup>,-P(0)R<sup>13</sup>R<sup>14</sup>;-PR<sup>13</sup>R<sup>14</sup>,-PR<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A;-P(OR<sup>13</sup>)OR<sup>14</sup>;-S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A;-N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; and NR <sup>13</sup> OR <sup>14</sup>; -NR <sup>13</sup> NR <sup>14</sup>R <sup>15</sup>; -CO<sub>2</sub>R <sup>13</sup>; OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR <sup>13</sup>R <sup>14</sup>; carbohydrate residue; and 155

have one or more carbons replaced by -O-; -NR<sup>13</sup>-; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A-; -S-; -SO-; acid; peptide; polypeptide; carbohydrate; polyether; or polyalkyl; wherein said carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR<sup>9</sup>-; -N<sup>+</sup>R<sup>9</sup>R <sup>10</sup>A<sup>-</sup>-; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R<sup>9</sup>A--; -PR<sup>9</sup>-; --SO2-; -S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>-; -PR<sup>13</sup>-; -P(O)R<sup>13</sup>-; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>-; phenylene; amino wherein the RX and RXA radicals comprising carbon optionally may phenylene; amino acid residue; peptide residue; polypeptide residue; P+R9R10A:; or -P(O)R9:; and 9

wherein R 18 is selected from the group consisting of alkyl; alkenyl; heterocyclylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; arylalkyl;

165

halogen; -CN; NO; oxo; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>+</sup>R<sup>9</sup>R<sup>11</sup>R<sup>12</sup>A<sup>-</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; be substituted with one or more radicals selected from the group consisting of wherein the R11 alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl;

130

175  $-SO_2R^9; -SO_3R^9; -CO_2R^9; -CONR^9R^{10}; -SO_2OM; -SO_2NR^9R^{10}; -PR^9R^{10}; -P(OR^{16})OR^{17}; -PO(OR^{16})OR^{17}; and -C(O)OM; and$ defined above; and wherein R?, R10, R11, R12, R13, R14, R15, R16, R17, R\*, A7, and M are as

80  $-NR^{7}_{-}$ ;  $-N^{\dagger}R^{7}R^{8}A^{-}$ ;  $-S^{-}$ ;  $-SO_{-}$ ;  $-SO_{2}$ ;  $-S^{\dagger}R^{7}A^{-}$ ;  $-PR^{7}$ ;  $-P(O)R^{7}$ ;  $-P(O)R^{7$ alkyne diyl; polyalkane diyl; alkoxy diyl; polyether diyl; polyalkoxy diyl; polypeptide residue; can optionally have one or more carbons replaced by -O-; polyalkoxy diyl; carbohydrate residue; amino acid residue; peptide residue; and alkene diyl; alkyne diyl; polyalkane diyl; alkoxy diyl; polyether diyl; carbohydrate; amino acid; and peptide; polypeptide; wherein alkane diyl; R19 is selected from the group consisting of alkane diyl; alkene diyl:

185 diyl; polyether diyl; polyalkoxy diyl; carbohydrate residue; amino acid residue; PTR 'R'A:; phenylene; heterocyclyl; quaternary heterocyclyl; or aryl; wherein alkane diyl; alkene diyl; alkyne diyl; polyalkane diyl; alkoxy

195 190 SO20M; -SO2NR <sup>13</sup>R <sup>14</sup>; -C(O)NK <sup>13</sup>R <sup>14</sup>; -C(O)OM; -COR <sup>13</sup>. P(O)R <sup>13</sup>R <sup>14</sup>; -PR <sup>13</sup>R <sup>14</sup>; -P <sup>†</sup>R <sup>13</sup>R <sup>14</sup>R <sup>14</sup>R <sup>14</sup>A; -P(OR <sup>13</sup>)OR <sup>14</sup>; -S<sup>\*</sup>R <sup>13</sup>R <sup>14</sup>A; and arylalkyl; halogen; oxo; -OR <sup>13</sup>; -NR <sup>13</sup>R <sup>14</sup>; -SR <sup>13</sup>; -S(O)R <sup>13</sup>; -SO<sub>2</sub>R <sup>13</sup>; -SO<sub>3</sub>R <sup>13</sup>; -NR <sup>13</sup>OR <sup>14</sup>; -NR <sup>13</sup>NR <sup>14</sup>R <sup>15</sup>; -NO<sub>2</sub>; -CO<sub>2</sub>R <sup>13</sup>; -CN; -OM; substituent groups independently selected from the group consisting of alkyl; alkenyl; alkynyl; polyalkyl; polyether; aryl; haloalkyl; cycloalkyl; heterocyclyl; peptide residue; and polypeptide residue can be substituted with one or more

wherein R?, R4, R11, R12, R13, R14 R13, and A are as defined above; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

- independently selected from the group consisting of hydrogen and alkyl. 122. A compound of claim 121 wherein R', R'A, R2, and R2A are
- independently selected from the group consisting of hydrogen and  $C_1$ - $C_{10}$  alkyl. A compound of claim 121 wherein R', R'A, R2, and R2A are
- independently selected from the group consisting of C2-C7 alkyl. A compound of claim 121 wherein R<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup>, and R<sup>2</sup> are

WO 00/47568

- independently selected from the group consisting of C2-C4 alkyl. A compound of claim 121 wherein R1, R14, R2, and R24 are
- independently selected from the group consisting of ethyl; n-propyl; n-butyl; and isobutyl. 126. A compound of claim 121 wherein R1, R14, R2, and R24 are
- wherein R<sup>9</sup> is as defined in claim 121. independently selected from the group consisting of hydrogen and -OR? 127. A compound of claim 121 wherein R3, R4, R4, and R44 are
- A compound of claim 126 wherein R9 is hydrogen.
- independently selected from the group consisting of hydrogen, alkyl and 129. A compound of claim 121 wherein R<sup>N</sup> and R<sup>NA</sup> are
- independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>10</sub>)alkyl and aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl. 130. A compound of claim 121 wherein R<sup>N</sup> and R<sup>NA</sup> are
- and benzyl. independently selected from the group consisting of hydrogen, methyl, ethyl 131. A compound of claim 121 wherein R<sup>N</sup> and R<sup>NA</sup> are
- dimethylamino. independently selected from the group consisting of methoxy and 132. A compound of claim 121 wherein one or more R" and R" are
- 133. A compound of claim 121 wherein q and r are each 1.
- hydroxy; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; independently selected from selected from the group consisting of halogen; 134. A compound of claim 121 wherein one or more Ry are

heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>; and -NR<sup>13</sup>C(O)R<sup>14</sup>;

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; haloC<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl;heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl;heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl;and polyether; or

2

wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyt; halo(C<sub>1</sub>-C<sub>10</sub>)alkyt; heterocyclyt; quaternary heterocyclyt; aryt(C<sub>1</sub>-C<sub>10</sub>)alkyt; heterocyclyt(C<sub>1</sub>-C<sub>10</sub>)alkyt; heterocyclyt(C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; heterocyclyt(C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; (C<sub>1</sub>-C<sub>10</sub>)alkyt; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyt; heterocyclyt; quaternary heterocyclyt; quaternary heterocyclyt; quaternary heterocyclyt(C<sub>1</sub>-C<sub>10</sub>)alkyt; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyt; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyt; coR<sup>16</sup>, NR<sup>9</sup>R<sup>10</sup>, NA<sup>7</sup>R<sup>9</sup>R<sup>10</sup>R<sup>W</sup>A<sup>7</sup>; and -CONR<sup>9</sup>R<sup>10</sup>, and

2

wherein R<sup>9</sup>, R<sup>10</sup> and R<sup>w</sup> are independently selected from the group

consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl;

(C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>
C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl;

carboxyheterocyclyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylamino; and acyl; and

wherein A is a pharmaceutically acceptable anion; and

wherein R<sup>11</sup> and R<sup>12</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or R<sup>11</sup> and R<sup>12</sup> together with the carbon atom to which they are attached form a cyclic ring:

23

form a cyclic ring; wherein  $\rm R^{16}$  and  $\rm R^{17}$  are independently selected from the group consisting of  $\rm R^9$  and M; and

wherein M is a pharmaceutically acceptable cation.

135. A compound of claim 121 wherein R<sup>19</sup> is selected from the group consisting of alkane diyl; polyalkane diyl; alkoxy diyl; and polyalkane diyl; wherein alkane diyl and polyalkane diyl can optionally have one or more carbons replaced by -O.; -NR<sup>7</sup>: -N<sup>7</sup>R<sup>8</sup>A-; -S.; -SO-; -SO-; -S<sup>4</sup>R<sup>7</sup>A-; -

WO 00/47568

PCT/US00/02503

8

 $PR^7$ ; -P(O)R $^7$ ; -P $^4R^7R^8A$ ·; or phenylene, wherein R $^3$  and R $^4$  are defined as in claim 121.

136. A compound of claim 121 wherein R<sup>19</sup> is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by -O.; -NR<sup>7</sup>.; -N<sup>7</sup>R<sup>8</sup>A·; -S·; -SO·; -SO<sub>2</sub>; -S<sup>4</sup>R<sup>7</sup>A·; -PR<sup>7</sup>; -P(O)R<sup>7</sup>; -P<sup>4</sup>R<sup>7</sup>R<sup>8</sup>A·; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; or polyalkyl, wherein R<sup>9</sup> and R<sup>10</sup> are defined as in claim 121.

137. A compound of claim 121 having the structural formula:

2

138. A compound of formula (V):

3

5

wherein:

2

q is an integer from 0 to 4;

r is an integer from 0 to 3;

t is an integer from 0 to 4;

u is an integer from 0 to 5;

20

alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; consisting of hydrogen; alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl;  $R^1$ ,  $R^2$ ,  $R^{1A}$ , and  $R^{2A}$  are independently selected from the group

and (polyalkyl)aryl; or  $\mathbb{R}^1$  and  $\mathbb{R}^2$  taken together with the carbon to which they are attached

heterocylcyloxyalkyl; heterocycloxyalkenyl; heterocyclyloxyalkynyl; alkylaryl;

25

form C3-C10 cycloalkyl or C3-C10 cycloalkenyl; form C<sub>3</sub>-C<sub>10</sub> cycloalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkenyl; or  $\mathbb{R}^{1A}$  and  $\mathbb{R}^{2A}$  taken together with the carbon to which they are attached

ဗ

aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; wherein the R<sup>1</sup>, R<sup>2</sup>, R<sup>1A</sup>, and R<sup>2A</sup> alkyl; cycloalkyl; alkenyl

heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may CN; halogen; oxo; -OR9; -NR9R10; -N+R9R10RWA; -SR9; -S+R9R10A; be substituted with one or more radicals selected from the group consisting of

35

WO 00/47568

CONR<sup>9</sup>R<sup>10</sup>; and p+R9R10RWA;-PR9R10;-S(O)R9;-SO2R9;-SO3R9;-CO2R9; and

alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; aryloxyalkynyl; heterocylcyloxyalkyl; heterocycloxyalkenyl; wherein the  $R^1$ ,  $R^2$ ,  $R^{1A}$ , and  $R^{2A}$  alkyl; cycloalkyl; alkenyl;

8

3 have one or more carbons replaced by -O-; -NR 9-; -N+R 9R 10A-; -S-; -SO-; -SO2-; -STR'A-; -PR'-; -P(O)R'-; -PTR'R10A-; or phenylene; and heterocyclyloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may

carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl carboxyalkylamino; alkoxyalkylamino; and acyl; and wherein  $\mathbb{R}^9$ ,  $\mathbb{R}^{10}$ , and  $\mathbb{R}^w$  are independently selected from the group

50

 $\mathbb{R}^3$ ,  $\mathbb{R}^4$ ,  $\mathbb{R}^{3A}$ , and  $\mathbb{R}^{4A}$  are independently selected from the group wherein A is a pharmaceutically acceptable anion; and

consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR<sup>9</sup>; -NR<sup>9</sup>R<sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; and -SO<sub>3</sub>R<sup>9</sup>; or

SS

-CR11R12; R3A and R4A together form =O; =NOR9; =S; =NNR9R10; =NR9; or R3 and R4 together form =O; =NOR9; =S; =NNR9R10; =NR9; or

=CR11R12;

S 8 -CONR<sup>9</sup>R<sup>10</sup>; or carboalkoyyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR<sup>9</sup>; -NR<sup>9</sup>R <sup>10</sup>; -SR<sup>9</sup>; -S(O)R<sup>9</sup>; -SO<sub>2</sub>R<sup>9</sup>; -SO<sub>3</sub>R<sup>9</sup>; -CO<sub>2</sub>R<sup>9</sup>; and heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; wherein  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  are independently selected from the group

form a cyclic ring; and  $\mathbb{R}^{11}$  and  $\mathbb{R}^{12}$  together with the carbon atom to which they are attached

wherein R<sup>9</sup> and R<sup>10</sup> are as defined above; and

consisting of halogen; -CN; -NO2; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary one or more  $R^{y}$  and  $R^{yA}$  are independently selected from the group

heterocyclyl; arylalkyl; heterocyclylalkyl; polyether, -OR<sup>13</sup>; -NR<sup>13</sup>R<sup>14</sup>

5

PCT/US00/02503

SR<sup>13</sup>;-S(O)R<sup>13</sup>;-SO<sub>2</sub>R<sup>13</sup>;-SO<sub>3</sub>R<sup>13</sup>;-NR<sup>13</sup>OR<sup>14</sup>;-NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>;- $CO_2R^{13}$ ; -OM; -SO2OM; -SO2NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR 13; -NR11C(O)R14; -NR11C(O)NR14R15; -NR11CO,R14; -OC(O)R11; OC(O)NR<sup>13</sup>R"; -NR<sup>13</sup>SOR"; -NR<sup>13</sup>SO<sub>R</sub>R"; -NR<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>; -P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -P(OR 13)OR 14; -S\*R 13R 14A; and -N\*R 13R 14R 15A; and

73

the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; optionally may be further substituted with one or more radicals selected from  $\begin{array}{l} \text{heterocycly!}, -OR^7; -NR^7R^8; -SR^7; -S(O)R^7; -SO_2R^7; -SO_3R^7; -CO_2R^7; -CONR^7R^8; -N^4R^7R^8R^9A; -P(O)R^7R^8; -PR^7R^8; -P^4R^7R^8R^9A; \text{ and} - CONR^7R^8; -PR^7R^8;  wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclylalkyl, and polyether substituents of the RY and RYA radicals alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary P(O)(OR7)OR3; and 8 82

optionally may have one or more carbons replaced by -O-; -NR7-; -N+R7R8A-: -S.; -SO.; -SO2-; -S\*R\*A-; -PR7.; -P(O)R7.; -P\*R7R8A-; or phenylene; wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, heterocyclylalkyl, and polyether substituents of the RY and RYA radicals alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, ᇤ

ಜ

wherein  $\mathbb{R}^{13}, \mathbb{R}^{14}$ , and  $\mathbb{R}^{15}$  are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; wherein  $\mathbb{R}^7$  and  $\mathbb{R}^8$  are independently selected from the group heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; 23

wherein R13 and R14 together with the nitrogen atom to which they are alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;

8

wherein R<sup>14</sup> and R<sup>15</sup> together with the nitrogen atom to which they are attached form a cyclic ring; and

50

PCT/US00/02503

wherein the  $R^{13}, R^{14},$  and  $R^{15}$  alkyl, haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quatemary heterocyclyl; arylalkyl;

radicals optionally may be substituted with one or more radicals selected from alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; 2

heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; OR<sup>16</sup>; NR<sup>9</sup>R<sup>10</sup>; NR<sup>9</sup>R<sup>16</sup>; SO<sub>3</sub>R<sup>16</sup>; SO<sub></sub> hydroxyalkyi; sulfoalkyi; alkenyi; alkynyi; aryi; heterocyclyi; quaternary CO2R<sup>16</sup>; -CONR<sup>9</sup>R<sup>10</sup>; -SO2NR<sup>9</sup>R<sup>10</sup>; -PO(OR<sup>16</sup>)OR<sup>17</sup>; -PR<sup>9</sup>R<sup>10</sup>  ${\rm P}^{+}{\rm R}^{9}{\rm R}^{10}{\rm R}^{11}{\rm A}_{\cdot\cdot\cdot\cdot}{\rm S}^{+}{\rm R}^{9}{\rm R}^{10}{\rm A}_{\cdot\cdot}$  and carbohydrate residue; and 3

wherein the R  $^{13}$  , R  $^{14}$  , and R  $^{15}$  alkyl; haloalkyl; cycloalkyl; polyalkyl; N+R9R10A: -S. -SO: -SO2: -S+R9A: -PR9: -P+R9R10A: -P(O)R9: alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR2-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; 120

polypeptide residue; and 125

wherein R 16 and R 17 are independently selected from the group wherein M is a pharmaceutically acceptable cation; and wherein n is 0, 1 or 2; and consisting of R9 and M; and 130

wherein R, R19, R11, R12, RW and A are as defined above; and

one or more RX and RXA radicals are independently selected from the  $R^{N}$  and  $R^{\mathsf{MA}}$  are independently selected from the group consisting of polyalkyi; haloalkyi; hydroxyalkyi; alkenyi; alkynyi; aryi; heterocyclyi; group consisting of hydrogen; halogen; -CN; -NO2; alkyl; cycloalkyl; hydrogen; alkyl; alkenyl; alkynyl; aralkyl; and heterocyclylalkyl; and 135

 ${\sf NR}^{\sf MC}({\sf O}){\sf R}^{13}$ , -C(O)OM; -C(OR $^{13}$ ; -OR $^{18}$ ; -S(O) $_{\sf D}{\sf NR}^{13}{\sf R}^{14}$ NR<sup>13</sup>OR<sup>14</sup>; -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>; -CO<sub>2</sub>R<sup>13</sup>; -OM; -SO<sub>2</sub>OM; -SO<sub>2</sub>NR<sup>13</sup>R<sup>14</sup>; quatemary heterocyclyl; aryialkyl; heterocyclylalkyl; polyether; acyloxy.-OR <sup>13</sup>,-NR <sup>13</sup>R <sup>14</sup>,-SR <sup>13</sup>, -S(O)R <sup>13</sup>, -S(O)R <sup>13</sup>, -S(O)R <sup>13</sup>, -SO<sub>3</sub>R <sup>13</sup>, -S<sup>+</sup>R <sup>13</sup>R <sup>14</sup>, 5

and carbohydrate residue;  $\mathrm{p^+R^{13}R^{14}R^{15}A^-}$ ; amino acid residue; peptide residue; polypeptide residue; -NR 13R 18; -NR 18OR 14; -N+R 13R 14R 15A; -PR 13R 14; -P(O)R 13R 14; -

145

150 S<sup>+</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>; and carbohydrate residue; and -NR9R10; -N+R9R10RWA; -SR16; -S(O)R9; -SO2R9; -SO3R16; -CO2R16 CONR 9R 10; -SO2NR 9R 10; -PO(OR 19)OR 17; -PR 9R 10; -P+R 9R 11R 12A; more radicals selected from the group consisting of halogen; -CN; oxo; -OR 16, hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy radicals optionally may be further substituted with one or wherein the RX and RX alkyl; cycloalkyl; polyalkyl; haloalkyl;

halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; be substituted with one or more radicals selected from the group consisting of wherein the RX and RXA quaternary heterocyclyl radical optionally may

155

polyether; -OR 13; -NR 13R 14; -SR 13; -S(O)R 13; -SO2R 13; -SO3R 13; -NR 13 OR 14; -NR 13 NR 14R 15; -CO2R 13; OM; -SO2OM; -SO2NR 13R 14; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl;

60 C(0)NR<sup>13</sup>R<sup>14</sup>; -C(0)OM; -COR<sup>13</sup>; -P(0)R<sup>13</sup>R<sup>14</sup>, -PR<sup>13</sup>R<sup>14</sup>; .

P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; -P(0R<sup>13</sup>)OR<sup>14</sup>; -S<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A; -N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A; and carbohydrate residue; and

or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; wherein the R<sup>X</sup> and R<sup>X</sup>, radicals comprising carbon optionally may have one or more carbons replaced by -O-; -NR  $^{13}$ ; -N<sup>+</sup>R  $^{13}$ A<sup>-</sup>; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>+</sup>R  $^{13}$ A<sup>-</sup>; -PR  $^{13}$ : -P(O)R  $^{13}$ -; -P<sup>+</sup>R  $^{13}$ R  $^{14}$ A-; phenylene; amino acid -S<sup>†</sup>R<sup>9</sup>A-; -PR<sup>9</sup>-; -P<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A-; or -P(O)R<sup>9</sup>-; and one or more carbons replaced by -O-; -NR<sup>9</sup>-; -N<sup>†</sup>R<sup>9</sup>R<sup>10</sup>A<sup>-</sup>-; -S-; -SO-; -SO<sub>2</sub>polypeptide residue; carbohydrate residue; and polyalkyl optionally may have residue; peptide residue; polypeptide residue; carbohydrate residue; polyether,

165

heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; wherein  $\mathbb{R}^{18}$  is selected from the group consisting of alkyl; alkenyl;

70

heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; be substituted with one or more radicals selected from the group consisting of arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radicals optionally may wherein the R 18 alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary

175

80 halogen; -CN; NO;; oxo;  $-0\dot{R}^9$ ;  $-NR^9R^{10}$ ;  $-N^+R^9R^{11}R^{12}A$ ;  $-SR^9$ ;  $-S(O)R^9$ ;  $-SO_2R^9$ ;  $-SO_2R^9$ ;  $-CO_2R^9$ ;  $-CO_3R^9$ ;  $-CO_$ 

wherein R9, R10, R11, R12, R13, R14, R15, R16, R17, Rw, A7, and M are as

190 185 PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A<sup>-</sup>-; phenylene; heterocyclyl; quaternary peptide residue; and polypeptide residue; can optionally have one or more carbohydrate residue; amino acid residue; peptide residue; and polypeptide carbons replaced by -O-; -NR '-; -NTR 'R 'A-; -S-; -SO-; -SO2-; -STR 'A-; diyl; polyether diyl; polyalkoxy diyl; carbohydrate residue; amino acid residue; residue; wherein alkane diyl; alkene diyl; alkyne diyl; polyalkane diyl; alkoxy alkyne diyl; polyalkane diyl; alkoxy diyl; polyether diyl; polyalkoxy diyl; R19 is selected from the group consisting of alkane diyl; alkene diyl;

heterocyclyl; or aryl; wherein alkane diyl; alkene diyl; alkyne diyl; polyalkane diyl; alkoxy

diyl; polyether diyl; polyalkoxy diyl; carbohydrate residue; amino acid residue;

200 195 P(O)R 13R 14; -PR 13R 14; -P+R 13R 14R"A; -P(OR")OR"; -S'R"R"A; and alkenyl; alkynyl; polyalkyl; polyether; aryl; haloalkyl; cycloalkyl; heterocyclyl; SO20M; -SO2NR<sup>13</sup>R<sup>14</sup>; -C(O)NR<sup>13</sup>R<sup>14</sup>; -C(O)OM; -COR<sup>13</sup>; -SO3R<sup>13</sup>, -NR<sup>13</sup>OR<sup>14</sup>, -NR<sup>13</sup>NR<sup>14</sup>R<sup>15</sup>, -NO2; -CO2R<sup>13</sup>, -CN; -OM; arylalkyl; halogen; oxo; -OR13; -NR13R14; -SR13; -S(O)R13; -SO2R13; substituent groups independently selected from the group consisting of alkyl; peptide; and polypeptide residue can be substituted with one or more

a pharmaceutically acceptable salt, solvate, or prodrug thereof. wherein R?, R1, R11, R12, R14, R15, and A are as defined above; or

independently selected from the group consisting of hydrogen and alkyl. 139. A compound of claim 138 wherein R!, R14, R2, and R24 are

independently selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>10</sub> alkyl 140. A compound of claim 138 wherein R', R', R2, and R2 are

independently selected from the group consisting of  $C_2$ - $C_7$  alkyl 141. A compound of claim 138 wherein R1, R14, R2, and R24 are

898

PCT/US00/02503

407

- 142. A compound of claim 138 wherein R¹, R¹, R¹, and R²^ are independently selected from the group consisting of  $C_2$ - $C_4$  alkyl.
- 143. A compound of claim 138 wherein R¹, R¹, R², and R², are independently selected from the group consisting of ethyl; n-propyl; n-butyl; and isobutyl.
- 144. A compound of claim 138 wherein R<sup>3</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>4</sup>A are independently selected from the group consisting of hydrogen and -OR\*, wherein R<sup>3</sup> is as defined in claim 138.
- 145. A compound of claim 144 wherein R9 is hydrogen.
- 146. A compound of claim 138 wherein  $\mathbb{R}^N$  and  $\mathbb{R}^{NA}$  are independently selected from the group consisting of hydrogen, alkyl and aralkyl.
- 147 A compound of claim 138 wherein  $R^N$  and  $R^{NM}$  are independently selected from the group consisting of hydrogen,  $(C_1-C_{10})$ alkyl and aryl $(C_1-C_{10})$ alkyl.
- 148. A compound of claim 138 wherein  $R^N$  and  $R^{MA}$  are independently selected from the group consisting of hydrogen, methyl, ethyl and benzyl.
- 149. A compound of claim 138 wherein one or more  $R^a$  and  $R^{aA}$  are independently selected from the group consisting of methoxy and dimethylamino.
- 150. A compound of claim 138 wherein q and r are each 1.
- 151. A compound of claim 138 wherein one or more R<sup>y</sup> are independently selected from selected from the group consisting of halogen; hydroxy; -NO2; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; ayl(C<sub>1</sub>-C<sub>10</sub>)alkyl;

WO 00/47568 PCT/US00/02503

408

heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; polyether; -OR  $^{13}$ ; -NR  $^{13}\mathrm{R}^{14}$ ; and -NR  $^{12}\mathrm{C}(\mathrm{O})\mathrm{R}^{14}$ ; and

wherein R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are independently selected from the group consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ap/l(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyliteterocyclyl(C<sub>1</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-C<sub>10</sub>-

- (C<sub>1</sub>-C<sub>10</sub>)alkylammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether; or wherein the R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> (C<sub>1</sub>-C<sub>10</sub>)alkyl;halo(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; c<sub>1</sub>-C<sub>10</sub>)alkyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; and polyether radicals
  - optionally may be substituted with one or more radicals selected from the group consisting of halogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; -OR<sup>16</sup>; -NR<sup>9</sup>R<sup>10</sup>; -N<sup>1</sup>R<sup>9</sup>R<sup>10</sup>R<sup>WA</sup>; and -CONR<sup>9</sup>R<sup>10</sup>; and wherein R<sup>9</sup> and R<sup>10</sup> are independently selected from the group
- 20 consisting of hydrogen; (C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; ammonium(C<sub>1</sub>-C<sub>10</sub>)alkyl; (C<sub>1</sub>-C<sub>10</sub>)alkyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carbo(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; carboxyleterocyclyl; carboxy(C<sub>1</sub>-C<sub>10</sub>)alkylamino; and acyl; and
- wherein A is a pharmaceutically acceptable anion; and
  wherein R 11 and R 12 are independently selected from the group
  consisting of hydrogen; (G<sub>1</sub>-C<sub>10</sub>)alkyl; heterocyclyl; aryl(C<sub>1</sub>-C<sub>10</sub>)alkyl;
  carboxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; and carbo(C<sub>1</sub>-C<sub>10</sub>)alkoxy(C<sub>1</sub>-C<sub>10</sub>)alkyl; or
  R 11 and R 12 together with the carbon atom to which they are attached
- form a cyclic ring;

  wherein R<sup>16</sup> and R<sup>17</sup> are independently selected from the group

ಜ

consisting of  $\mathbb{R}^9$  and M; and wherein M is a pharmaceutically acceptable cation.

152. A compound of claim 138 wherein R<sup>19</sup> is selected from the group consisting of alkane diyl; polyalkane diyl; alkoxy diyl; and polyalkane diyl; wherein alkane diyl and polyalkane diyl can optionally have one or more carbons replaced by -O-; -NR<sup>7</sup>; -N<sup>+</sup>R<sup>7</sup>R<sup>8</sup>A-; -SO-; -SO-; -SO<sub>2</sub>··-S<sup>+</sup>R<sup>7</sup>A-; -

PCT/US00/02503

ŝ

PR  $^2$ ; -P(O)R  $^2$ ; -P<sup>+</sup>R  $^2$ R  $^8$ A:; or phenylene, wherein R $^2$  and R $^4$  are defined as in claim 138.

153. A compound of claim 138 wherein R<sup>19</sup> is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by -O-; -NR<sup>7</sup>-; -N<sup>4</sup>R<sup>7</sup>R<sup>8</sup>A-; -S-; -SO-; -SO<sub>2</sub>-; -S<sup>4</sup>R<sup>7</sup>A-; -PR<sup>7</sup>-; -P(O)R<sup>7</sup>-; -P<sup>4</sup>R<sup>7</sup>R<sup>8</sup>A-; phenylene; amino acid; peptide; polypeptide; carbohydrate; or polyalkyl, wherein R<sup>9</sup> and R<sup>10</sup> are defined as in claim 138

154. A compound of claim 138 having the formula:

155. A pharmaceutical composition comprising an antihyperlipidemic effective amount of a compound of formula (I) of claim 1; and a pharmaceutically acceptable carrier.

WO 00/47568 PCT/US00/02503

410

- 156. A pharmaceutical composition comprising an antiatherosclerotic effective amount of a compound of formula (I) of claim 1; and a pharmaceutically acceptable carrier.
- 157. A pharmaceutical composition comprising an antihypercholesterolemia effective amount of a compound of formula (I) of claim 1; and

a pharmaceutically acceptable carrier.

- 158. A pharmaceutical composition comprising an antihyperlipidemic effective amount of a compound of formula (I) of claim 2; and a pharmaceutically acceptable earrier.
- 139. A pharmaceutical composition comprising an antiatherosclerotic effective amount of a compound of formula (I) of claim 2; and a pharmaceutically acceptable carrier.
- 160. A pharmaceutical composition comprising an antihypercholesterolemia effective amount of a compound of formula (I) of claim 2; and

a pharmaceutically acceptable carrier.

- 161. A method for the prophylaxis or treatment of a hyperlipidemic condition comprising administering to a patient in need thereof a composition of claim 155 in unit dosage form.
- 162 A method for the prophylaxis or treatment of an atherosclerotic condition comprising administering to a patient in need thereof a composition of claim 156 in unit dosage form.
- 163. A method for the prophylaxis or treatment of hypercholesterolemia comprising administering to a patient in need thereof a composition of claim 157 in unit dosage form.

PCT/US00/02503 WO 00/47568

41

- condition comprising administering to a patient in need thereof a composition A method for the prophylaxis or treatment of a hyperlipidemic of claim 158 in unit dosage form. <u>2</u>
- A method for the prophylaxis or treatment of an atherosclerotic condition comprising administering to a patient in need thereof a composition of claim 159 in unit dosage form. 165.
- hypercholesterolemia comprising administering to a patient in need thereof a A method for the prophylaxis or treatment of composition of claim 160 in unit dosage form. 166

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau





PCT (43) International Publication Date 17 August 2000 (17.08.2000)

(74) Ageuts: WARNER, James, M. et al.; G.D. Searle & Co., Corporate Patent Department, \$200 Old Orchard Read, Stokie, IL 60077 (US).

C07D 281/02,

(51) International Patent Classification?; A61K 31/55, A61P 306, C07D 417/12

- English English (21) International Application Number: PCT/US00/02503 (22) International Filing Date: 10 February 2000 (10.02.2000)
- (84) Designated States (regional): ARIPO patrat (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, JT, LU, MC, ML, FT, SD, OAPI patent (BF, BJ, CF, CG, CJ, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

S

12 February 1999 (12.02.1999)

(30) Priority Data: 60/119,933

(26) Publication Language: (25) Filing Language:

Published

(71) Applient ffor all designated States except USJ; G.D. SEARLE & CO. [US/US]; Corporate Patent Department, 5200 Old Orchard Road, Stokie, IL 60077 (US).

Inventors; and

55

With international search report.

(88) Date of publication of the international search report: 14 December 2000 9) Inventors/Applicants (for US only); TOLLEFSON, (g Michael, B. (USCUS); 337 Big Hom Drive, Hainesville, IL 6030 (US), KOLODZIEJ, Steve, A. (USUS); 2448 Carjon Road, Ballwin, MO 63021 (US), REITZ, David, F B. (USVUS); 14814 Pleasant Ridge Court, Chesterfield, MO 63017 (US).

For modester codes and other abbraviations, refer to the "Guid-once Nates on Codes and Abbraviations" appearing at the begin-ning of each regular issue of the PCT Gazette.

96
(94) Title: 1.2-BENZOTHIAZEPINES FOR THE TREATMENT OF HYPERLIPUBMIC DISEASES
(95) Title: 1.2-BENZOTHIAZEPINES FOR THE TREATMENT OF HYPERLIPUBMIC DISEASES
(97) Abstract: Novel 1.1-dioxido-1.2-beamothiazepines, derivatives and analogs thereof, pharmaceutical compositions containing
(97) the inches is medicine, particularly in the prophylaxia molor treatment of hyperlipideentic diseases, conditions analor disyear, and their use in medicine, particularly in the prophylaxia molor treatment of hyperlipideentic diseases, conditions analor disyear, and their use in medicine, particularly in the prophylaxia molor treatment of hyperlipideentic diseases, conditions analor dis-

2

## INTERNATIONAL SEARCH REPORT

**Comment defining the general state of the st which is not collect to understand the dot in contrible with in application but collect to understand the principle of theory tradehylo be invested to the distribution of the state of the stat	X   Futber documents are titled in the continuation of box C.   X   Patent family members are titled in arrans.  Special categories of cited documents:	· -/	WO 96 16051 A (WELLCOME FOUND ;BRIEADDY LAWRENCE EDWARD (US); HANDLON ANTHONY LOU) 30 May 1996 (1996-05-30) cited in the application claim 1	WO 98 02432 A (SUGIURA YOSHIHIRO :DOI TAKAYUKI (JP); KATO KANEYOSHI (JP); KAWADA) 22 January 1998 (1998-01-22) Cited in the application Claim 8	WO 98 38182 A (GLAXO GROUP LTD ;HANDLON 1-103 ANTHONY LOUIS (US); HODGSON GORDON LEWIS) 3 September 1998 (1998-09-03) Formula (Ie) claims 1,6	Catagory Citation of document, with indication, where appropriate, of the relevant passages Relevant to ct	<b>⊣</b> ≅	Electronic data tosse consulted during this international search (numbe of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data	Commission salithed ones than minimum documentation to the extent that such documents are included in the fields searched	IPC 7 CO7D A61K	R. FELDS SEARCHED	o to the matter of the first that the matter of the first that the	107,00	PCT/US 00/02503
repolication to a	NHK.		1-103		1-103	Relevant to claim No.			a.				2000	2502

page 1 of 2

## INTERNATIONAL SEARCH REPORT

PCT/US 00/02503

>	Catagory *
WO 96 05188 A (WELLCOME FOUND ; BRIEADDY LAWRENCE EDWARD (US)) 22 February 1996 (1996-02-22) cited in the application	Category Citation of document, with indication, where appropriate, of the relevant passages
1-103	Relevant to claim No.

page 2 of 2

## INTERNATIONAL SEARCH REPORT

9616051 A 22-01-1998 AU 6823898 A 9616051 A 22-01-1998 AU 3460797 A 9616051 A 30-05-1996 AU 3460797 A 9616051 A 30-05-1996 AT 189891 T AU 3466797 A 10338672 A 104712	A 03-09-1998 AU 6823898 A  A 22-01-1998 AU 3460797 A  A 30-05-1996 AT 189891 T  AU 3462795 A  AU 3462797 A  AU 346299 A  BR 9509683 A  CZ 9701473 B  BR 9509683 A  CZ 9701473 A  AU 426096 A  BR 9509686 A  CZ 970126 A  AU 426096 A  BR 9509886 A  CZ 970120 A  AU 426096 B  BR 9509886 A  CZ 970137 A  AU 426096 A  BR 9508886 A  CZ 970137 A  AU 77129		Info	Information on patent family member	Ę	PCT/US	International Application No PCT/US 00/02503	
9838182 A 03-09-1998 AU 6823898 A 9616051 A 22-01-1998 AI 13460797 A 9616051 A 30-05-1996 AT 138981 T 706325 B AU 346295 A 10338672 A 10338672 A 10338672 A 10338672 A 10338672 A 10338672 A 1032588 A 1032588 A 1032588 A 103268 A 103268 A 103269  A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 103269 A 103269 A 103269 A 103269 A 103269 A 1032699 A 103269 A 10	9802432 A 03-09-1998 AU 6823898 A 9802432 A 22-01-1998 AU 3460797 A 9616051 A 30-05-1996 AT 189891 T AU 3876295 A BU 585058 A BU 585058 A BU 585058 A BU 585073 B BU 585078 B BU 585073 B BU 585078 B BU 585073 B BU 585079 B BU 58507	Patent document lted in search repor	-	Publication date	-	Patent family member(s)	Publicatio	
9602432 A 22-01-1998 AU 3460797 A 9616051 A 30-05-1996 AT 189891 T AU 706325 B R 9509683 A CZ 9701473 A CZ 29446 A CZ	9616051 A 30-05-1996 AI 183891 T	WO 9838182	⋖	03-09-1998	₹	1	18-09-	
A 30-05-1996 AT 189391 T AU 706325 A BR 9509683 A CZ 9701473 A CZ 9701477 A CZ 970147 A	9616051 A 30-05-1996 AT 1189891 T AU 706325 B AU 3676295 A BR 8 8 3676295 A BR 9509683 A CZ 9701473 B CF 0792268 A ES 2144151 T FT 972085 A HU 77412 A JP 11500102 T NO 972261 A HU 277412 A HU 277412 A HU 277412 A HU 277412 A HU 277512 A HU 277512 A HU 77712 A HU 777129	40 9802432	∢ .	<u></u>	₹5	3460797 0338672	09-02-	8661
9605188 A 22-02-1996 AP 720 A AU 696073 B AU 4426096 A BE 62048 B 6 62048 B 6 101209 A BR 950886 A CA 2197099 A CZ 970073 A F1 97037 A F1 114877 A JP 12935756 B JP 10504035 T NO 970585 A NO 970585 A SK 17797 A SK 17797 A	9605188 A 22-02-1996 AP 7720 A  AU 696073 B  AU 4426096 A  BG 62048 B  BG 62048 B  BG 62048 B  BG 775129 A  CA 2197099 A  CA 219709 A  CA 21970	96160	∢ .	5-199	C7284211111111111111111111111111111111111		15-03- 17-06- 17-06- 18-08- 18	2000 11999 11997 1200 1200 1200 1200 1200 1200 1200 120
			⋖	22-02-1996	A P R S & S & S & S & S & S & S & S & S & S	720 A 696073 B 4426096 A 62048 B 101209 A 9508586 A 2197099 A 970373 A 970531 A 970531 A 970531 A 77129 A 116504035 T 2935756 B 220911 A 318496 A 318496 A 17797 A		1999 1999 1999 1999 1999 1999 1999 199
						+		

INTERNATIONAL SEARCH REPORT

International application No. PCT/US 00/02503

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first aheat)	
This international Search Report has not been established in respect of certain claims under Anticle 17(2)(a) for the following reasona:	
<ol> <li>X Caloura Nos.: because they relate to subject matter not required to be searched by this Authority, namely:         Allthough claims 161-166 are directed to a method of treatment of the         human/animal body, the search has been carried out and based on the alleged         effects of the compound/composition.</li> </ol>	
2. X claims loos.: 104-154 -all other claims only searched partially because they rete to para of the international Application has do not comply with the prescribed requirements to each en extent that no meaningful International Search can be centred out, specifically; see FURTHER INFORMATION sheet PCT/ISA/210	
3. Userian Nos.: Declaras they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	1
This international Searching Authority found multiple inventions in this international application, as tollows:	
1. As all required additional search less were timely paid by the applicant, this international Search Report covers all	
2. I As all asarchable claims could be searched without effort justifying an additional lee, this Authority did not finite payment of any additional lee.	
3. As only some of the required additional bearch fees were timely paid by the applicant, this international Search Report . Oovers only those claims for which fees were paid, specifically claims Nos.:	
<ol> <li>Instructed additional search lees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.</li> </ol>	
Remark on Protest  The additional search less were accompanied by the applicant's protest.  No protest accompanied the payment of additional search less.	

Form PCTASA210 (continuation of first sheet (1)) (July 1998)

International Application No. PCTUS 00 02503

FURTHER INFORMATION CONTINUED FROM PCT/ISAJ 210

Continuation of Box I.2

Claims Nos.: 104-154 -all other claims only searched partially

Present claims 1-166 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations (e.g. prodrug), huge definitions (such as hydrocarbyl or containing at least one heteroatom) and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely those compounds recited in the physically characterised and tested examples 1-24 on pages 284-327 and closely related homologous compounds as defined in the next paragraph. It is noted that only compounds of the formula (I) appear to have been exemplified and that there are no examples of formulae (III). (IV) or (V). It should be noted that only examples which are clearly defined and physically characterised have been taken into consideration. Examples 10-1652 do not appear to be be defined as regards the RN substituent and are therefore not examples which are adequately defined for supporting the scope of the claims.

The search has been limited to the examples and a generalisation thereof to compounds of formula (I) in which R3 and R4 are H and OH, R5 is hydrogen and R6 is a (substituted) phenyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCI). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.